EVIDENCE FOR ACTION TECHNICAL PAPERS

EFFECTIVENESS OF STERILE NEEDLE AND SYRINGE PROGRAMMING IN REDUCING HIV/AIDS AMONG INJECTING DRUG USERS

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CONTENTS

PREFACE

The global environment for a response to HIV has shifted substantially towards a massive scaling up of prevention, treatment and care interventions. In particular, the world made an unprecedented commitment during the United Nations Special Session on HIV/AIDS in 2001 to halting and reversing the epidemic by 2015. In support of this, additional resources to fund an expanded response have been come available through the Global Fund to Fight AIDS, Tuberculosis and Malaria.

Countries face the challenge of translating these commitments into practical programmes, including a range of comprehensive interventions to address HIV transmission related to injecting drug use. Although a huge body of scientific literature details the effectiveness of interventions, public health professionals often experience difficulties in accessing and interpreting this knowledge base.

This publication, together with other Evidence for Action technical papers, aims to make the evidence for the effectiveness of selected key interventions in preventing HIV transmission among injecting drug users accessible to a policy-making and programming audience. The interventions reviewed range from providing information and sterile injecting equipment to the impact of drug dependence treatment on HIV prevention. Each publication summarizes the published literature and discusses implications for programming with a particular focus on resource-limited settings.

1. INTRODUCTION

Following an epidemic of hepatitis B and hepatitis C (and HIV as discovered later) among injecting drug users (IDUs) in Edinburgh, Scotland between 1982 and 1984, a pharmacist decided to provide sterile injecting equipment, a decision that was soon overruled by authorities [1].

After an outbreak of hepatitis B among IDUs in Amsterdam in 1983, an organization of IDUs asked municipal health authorities to provide sterile injection equipment [2]. This request was initially rejected but the decision was soon reversed, allowing for the establishment of the first official needle syringe programme in the world. The HIV/AIDS pandemic soon became the rationale for this programme and similar programmes were rapidly established in many other parts of the world. Needle syringe programmes now operate officially in over 40 countries. Evaluation of the effectiveness and safety of these programmes began soon after they were first established and a vast literature was rapidly generated.

Providing access to and encouraging utilization of sterile needles and syringes for IDUs is now generally considered to be a fundamental component of any comprehensive and effective HIV-prevention programme. A wide variety of measures have been developed to improve access to and utilization of sterile injecting equipment, including needle syringe programmes (NSP), strategies for disinfecting needles and syringes where they are reused or shared, pharmacy-based distribution, sale or exchange schemes, vending machines and other distribution programmes, policies and programmes to encourage more appropriate disposal of used needles and syringes and injecting paraphernalia legislation. Much effort has been expended on improving knowledge, changing attitudes and reducing risk behaviour, but unless the means for behaviour change also become more readily available, improved knowledge and attitudes will not result in reduced risk. Likewise, unless efforts to increase access to sterile injecting equipment are buttressed by other efforts to support behaviour change, risk reduction will remain unaffected. Interventions to improve access to sterile injecting equipment have been implemented in many countries throughout the developed world and to a lesser extent in transitional and developing countries. In the absence of an effective and widely deployed vaccine against HIV, measures to improve access to sterile needles and syringes will remain the most effective tool available to reduce the spread of this virus among (and from) IDUs.

This review examines whether sterile needle and syringe programmes have been demonstrated scientifically to reduce the spread of HIV among IDUs. The evidence is evaluated for the first time according to the criteria originally proposed by Bradford Hill [3] to allow a causal relationship to be inferred from observed associations. Several additional criteria, which focus on the feasibility and sustainability of interventions, rather than causality, have been added subsequently by various authors.

The reliability of research conclusions without support from randomized controlled clinical trials in both clinical medicine and public health is often questioned. However, the difficulty of conducting a strictly randomized controlled trial to evaluate a public health intervention such as a NSP should not be underestimated [4, 5]. Potential sources of bias and confounding are impossible to control because of insurmountable ethical and logistical impediments. For example, in countries and states where NSPs are illegal, IDUs who attend these facilities are known to differ substantially in terms of socioeconomic characteristics and drug use patterns (such as frequency of injecting and needle-sharing) compared to other IDUs who do not attend these facilities.

Furthermore, randomization of IDUs in jurisdictions where NSPs are illegal is fraught with virtually overwhelming legal, ethical and logistical obstacles. Where NSPs operate legally, ethical and logistical problems of randomizing IDUs to NSP use or non-use prevail as denial of access (to a control group) is a major insurmountable issue. In the absence of randomization, some other major methodological problems become even more significant, including the accurate measurement of needle-sharing and injection frequency. In addition, evaluation studies have inevitably been conducted at different stages of HIV epidemics with wide variations in seroprevalence and seroincidence. Where seroprevalence is low, an evaluation may fail to detect effective HIV prevention because so few infections occur. Where evaluation is conducted in high seroprevalence settings, studies may fail to detect effective prevention by NSPs because many infections are sexually transmitted.

In addressing these methodological concerns, a report from the United States National Academy of Sciences' Institute of Medicine concluded that to reject NSPs, based on limitations of the design of single studies, ignores both the preponderance and pattern of the evidence and 'is both poor scientific

judgment and bad public health policy' [6]. The Institute argued 'that the improbability of being able to carry out the definitive study… does not necessarily preclude the possibility of making confident scientific judgments' and (citing the words of the biostatistician A. Bradford Hill) that 'incomplete' scientific evidence 'does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand'. Bradford Hill argued that if certain criteria are met in a number of observational studies evaluating an association, then there is an increased probability that a statistical association is causal.

The criteria proposed by Bradford Hill to infer causality are: strength of association, replication of findings (or consistency), specificity of association, temporal sequence, biological plausibility of the association, biological gradient (or a dose–response relationship), coherence with established facts or other knowledge, experimental evidence (if available) and argument by analogy [3]. Although originally proposed for observational studies, in recent years these criteria have increasingly been used to assess evidence from studies evaluating interventions. The original criteria and five additional criteria, (unanticipated benefits, cost-effectiveness, absence of negative consequences, special populations and feasibility of implementation and coverage) will be applied to all of the terms of reference of this project (see below), although the literature for some interventions is not nearly as extensive as that for evaluating NSPs.

1.1 Terms of reference

The general brief for this report was to evaluate the evidence on the effectiveness of sterile needle and syringe programming (including other injecting paraphernalia) for HIV prevention among IDUs in different settings and contexts, and to recommend how the evidence can guide public health policy-makers in programming for HIV prevention among IDUs. The report was to include all of the following subcategories:

- needle and syringe decontamination strategies;
- needle and syringe exchange;
- pharmacy, vending and other distribution programmes;
- needle and syringe disposal; and
- injecting paraphernalia legislation.

In addressing the key section of the paper, evidence on effectiveness, reference should be made to crucial studies that examine the effectiveness and cost-effectiveness of specific interventions. For each key study, descriptions should be provided of the study, methodology, sampling, outcomes, study limitations, interpretation and how easily findings can be generalized, with a comment on standard of proof. Less rigorous studies may be referred to in order to illustrate certain points not covered in other studies or to raise issues for further investigation. Recommendations should be made for further studies if necessary. Finally, every effort should be made to ensure coverage of the international literature, including grey literature, by including (bi-/multi-lingual) co-authors who are able to access non-English language literature and can access grey literature from different global regions.

2. METHODOLOGY

A search of the published scientific literature was carried out using Medline data bases and International Pharmaceutical Abstracts, supplemented by online bibliographies such as those produced by the Drug Policy Alliance [7, 8] and the United States Department of Health and Human Services [9]. The search for NSP literature exploded the keywords needle and syringe exchange, HIV infections and substance abuse, intravenous. Literature on bleach and decontamination was identified by exploding the keywords disinfection, HIV infections and acquired immunodeficiency syndrome for the period 1989–2002. The result was then combined with each of the keywords substance abuse (intravenous), syringes and needles. Separate searches were performed for syringe disposal, pharmacy and vending distribution and legislation by exploding and combining the keywords needles, syringes, pharmacy, pharmacists, vending machines, legislation and substance abuse (intravenous). Several comprehensive reviews on the effectiveness of needle and syringe exchange [6-10] and on bleach and decontamination strategies [6, 11] were also drawn on extensively. Conference abstracts were reviewed, and searches of the Internet were conducted, especially for the first, third, fourth and fifth terms of reference, but resources were not available to permit hand searching of other grey literature.

The Bradford Hill guidelines or causal criteria were identified as an appropriate framework to evaluate the literature on each of the five topics [3, 12] and further reference was made to Spitzer for their definition and application [13]. Five additional criteria (cost-effectiveness, absence of negative consequences, unanticipated benefits, feasibility of implementation and coverage, and special populations) were also applied in view of their applicability to public health interventions.

The null hypothesis used for this study was that measures to increase the availability and utilization of sterile injecting equipment, disinfection or bleach decontamination of injecting equipment do not reduce HIV risk behaviour, HIV seroprevalence or HIV seroincidence of IDUs.

The criteria were categorized as either Bradford Hill causal criteria or additional feasibility and implementation criteria. The criteria were defined as follows:

A. Bradford Hill causal criteria

Strength of association. The strength of a supposed association between an exposure factor and an outcome is gauged by the appropriate statistic used to measure the protective effect of an intervention. The preferred statistic, where available, is relative risk (RR) or odds ratio (OR) with associated confidence intervals.

Replication of findings. Also referred to as "consistency", this criterion examines whether different studies conducted in different locations by different investigators have reported similar findings.

Specificity of association. Specificity is said to be present when the alleged exposure factor (or intervention) is exclusive to the outcome and when the outcome has no other known cause or associated risk factors. For example, have NSPs had the unique effect of reducing HIV incidence, or have they had multiple other effects? And has a reduced seroincidence only occurred in locations where NSPs have been introduced?

Temporal sequence. For a cause-and-effect relationship to be supported, was the introduction of an intervention followed by a reduction in the outcome factor? Did the introduction of NSPs precede a reduction in needle-sharing, other risk behaviours or HIV incidence? Conversely, in locations where NSPs were closed, did risk behaviour and HIV incidence increase subsequently?

Biological plausibility. This criterion refers to the presence or absence of a likely biological mechanism linking the risk exposure or intervention to the observed findings.

Biological gradient. Evidence that increasing exposure to an intervention or risk factor results in a commensurate positive or negative change in an outcome is indicative of a biological gradient.

Experimental evidence. This criterion often provides the strongest support for causation and examines whether preventive action, in this case increased availability and utilization of sterile injecting equipment, actually reduces needle-sharing, which in turn reduces HIV incidence and/or prevalence.

Reasoning by analogy. Causality is supported by analogy if there are similar associations or causal relationships in other clinical or epidemiological areas of relevance. This may involve 'apposite' studies where, say, NSP use leads to lower HCV or HBV incidence compared to non-NSP use.

Coherence. When the evidence from different disciplines and different sources "hangs well together", this criterion is considered to be fulfilled. For example, lack of supportive laboratory findings would count against coherence. Are there documented examples of HIV incidence declining without NSPs? Does the apparently lower impact of NSPs on HCV incidence damage the evidence for effective HIV prevention?

B. Additional feasibility and implementation criteria

Cost effectiveness. Although estimated in a number of different ways, authorities pay increasing attention these days to the magnitude of benefit achieved from allocation of scarce public resources. Is the introduction of NSPs and other interventions cost-effective in all parts of the world and at different stages of an HIV epidemic?

Absence of negative consequences. Consideration of possible inadvertent adverse consequences is an important part of evaluating clinical and public health interventions. The presence of unintended negative consequences has a major impact on adoption or expansion of interventions. Fear that increased availability of sterile needle syringe programmes might exacerbate illicit drug use has been a major factor delaying adoption and expansion of these programmes.

Feasibility of implementation, expansion and coverage. Is it feasible to implement NSPs in diverse settings, including resource-poor settings, and to expand these to a scale commensurate with public health need?

Unanticipated benefits. Does the introduction of NSPs lead to other unintended and welcome benefits (such as increased referral to drug treatment)?

Special populations. How successful are NSPs in reaching special populations that have been identified as particularly at risk (such as young IDUs) or of considerable public health significance (such as 'bridge populations' like homosexual male IDUs or commercial sex workers who also inject drugs)?

3. RESULTS

3.1 The effectiveness of bleach and decontamination strategies

3.1.1 Strength of association HIV:

Three field studies (resulting in four reports) assessing the effect of bleach as a disinfectant for injecting equipment on HIV seroprevalence among IDUs [14-17] (Table 1) concluded that disinfection of needles with bleach appeared to offer no protection, or at best little protection, against HIV infection. The study populations were small and the measures of association had wide confidence intervals. Moreover, two studies assessed the effect of bleach on HCV prevalence [18, 19] and neither found a significant protective effect of bleach on HCV seroconversion. At best, one of the studies [18] suggests a small (and probably insignificant) reduction of HCV infection.

There is insufficient evidence to consider that the criterion of 'strength of association' has been fulfilled.

3.1.2 Replication of findings

All three field studies that were identified [14-17] concluded that the use of bleach did not offer adequate protection against HIV infection. (The laboratory evidence, in contrast, suggests disinfection with bleach can, under certain conditions, provide protection against HIV).

There is insufficient evidence to consider that the criterion of 'replication of findings' has been fulfilled.

3.1.3 Specificity of association

The cleaning of needles and syringes does not have a unique impact on reducing HIV infection among IDU because this intervention might reduce infection with all other types of micro-organisms. Numerous factors affect HIV transmission among IDUs and cleaning of injection equipment takes place in many different ways: for example, it has been shown that sharing of paraphernalia other than needles may modify infection rates [20-21], and adherence to cleaning protocols is often poor [22, 23].

There is insufficient evidence to consider that the criterion of 'specificity of association' has been fulfilled.

3.1.4 Temporal sequence

As insufficient evidence was found to support strength of association; it is not surprising that no relevant literature on temporal sequence was identified.

There is insufficient evidence to consider that the criterion of 'temporal sequence' has been fulfilled.

3.1.5 Biological plausibility

HIV detected in used syringes, and remains viable (i.e. can infect subsequent persons)

The link between HIV infection and subsequent development of AIDS has been conclusively demonstrated. It has also been shown that HIV-1 is present in blood contaminated needles and syringes (particularly if visibly contaminated) from IDUs [21, 24-26]. Furthermore, HIV remains viable at room temperature for up to four weeks [27]. It is well accepted that HIV can be transmitted by injection of infected blood [28]. Sharing of syringes and needles is also a common behaviour: in an Australian study of NSPs, 31% of respondents were found to have shared a syringe in the previous month [29]. A similar proportion of IDUs (35%) in New Haven, United States of America admitted to sharing needles before an NSP was introduced [30]. Higher proportions have been reported among IDUs in prisons [31, 32]. It has also been shown that those IDUs who share needles have higher rates of HIV antibodies [33].

Bleach (hypochlorite) is an effective disinfectant

The efficacy of bleach as a disinfectant for inactivating HIV has been shown in numerous laboratory studies [34-50]. These studies, summarized in Table 2, may not all be directly comparable, having used different simulated environments, virus and/or culture medium types, viral loads and activation measures. However, there is general agreement that bleach can be effective in inactivating HIV. Higher concentrations of bleach, although not always necessary, are more effective. Contact time with bleach and the presence of other matter, such as clotted blood in syringes, are also important factors influencing efficacy.

There is sufficient evidence to consider that the criterion of 'biological plausibility' has been fulfilled.

3.1.6 Biological gradient

A biological gradient for the efficacy of bleach in inactivating HIV has been shown in laboratory studies only. However, no biological gradient has been demonstrated in field studies.

There is insufficient evidence to consider that the criterion of 'biological gradient' has been fulfilled.

3.1.7 Coherence of the evidence

The evidence for biological plausibility (see above) is a very strong foundation for this criterion. However, the lack of evidence in field studies is a significant weakness. Several factors may account for the lower efficacy of bleach observed in the field compared to the laboratory:

a) Other paraphernalia: shared needles and syringes is not the only source of potentially infectious material. Sharing of injection paraphernalia (e.g. water, spoons, filters, tourniquets and swabs) is common and may influence infection rates [20, 21].

b) Poor cleaning techniques: adherence to cleaning protocols is often inadequate even when cleaning guidelines have been disseminated widely [22, 23].

There is insufficient evidence to consider that the criterion of 'coherence of the evidence' has been fulfilled.

3.1.8 Experimental evidence

No relevant literature was identified.

There is insufficient evidence to consider that the criterion of 'experimental evidence' has been fulfilled.

3.1.9 Reasoning by analogy

Cleaning and sterilization of equipment for multiple use by multiple users: cleaning and sterilizing of equipment for use during surgical procedures is safe and well accepted. However, in surgical settings there are clearly defined practices and numerous safeguards to ensure adequate compliance. On occasions when infection control practices have not been followed infection has been a risk for subsequent patients.

Cleaning of equipment by lay persons outside healthcare settings: such as the disinfection of contact lenses.

There is sufficient evidence to consider that the criterion of 'reasoning by analogy' has been fulfilled.

3.1.10 Cost effectiveness

No relevant literature was identified.

There is insufficient evidence to consider that the criterion of 'cost effectiveness' has been fulfilled.

3.1.11 Absence of negative consequences

Although high concentrations of bleach reduced culture target cell viability and p24 antigen production in a laboratory study [51], lower concentrations did not reduce target cell viability and appeared to permit HIV-1 infection and replication in cell cultures. These lower concentrations would be similar to those left in syringes after cleaning, and may provide a false sense of security regarding the risk of HIV infection for drug injectors.

Accidental injection of bleach remaining in needles and syringes is believed to be non-toxic. External contact produces only minor local irritation. Eye exposure requires copious irrigation. Although massive ingestion can cause abdominal distress, caustic injury and hyperchloremic acidosis [52], IDUs would not normally be exposed to such accidental ingestion.

There is sufficient evidence to consider that the criterion of 'absence of negative consequences' has been fulfilled.

3.1.12 Feasibility of implementation, expansion and coverage

Several studies have shown that with proper education, IDUs can follow protocols for use of bleach [23, 53-55].

There is sufficient evidence to consider that the criterion of 'feasibility of implementation, expansion and coverage' has been fulfilled.

3.1.13 Unanticipated benefits

No relevant literature was identified.

There is insufficient evidence to consider that the criterion of 'unanticipated benefits' has been fulfilled.

3.1.14 Special populations

Correctional inmates: Drug injection and HIV infection are both common in jails and prisons [56, 57]. HIV has been shown to be transmitted in prison populations [32, 58]. Despite the official adoption of policies to make bleach available to inmates, disinfectant availability for inmates may be poor [57]. Few other HIV-prevention measures are available to inmates (including NSPs).

There is sufficient evidence to consider that the criterion of 'special populations' has been fulfilled.

3.2 The effectiveness of needle syringe programmes

3.2.1 Strength of association

There were 45 studies dating from 1989 to 2002 that were identified with NSP implementation as an intervention and HIV seroconversion, HIV seroprevalence or HIV risk behaviours among IDUs examined as outcome variables. Some studies assessed multiple outcomes. Out of 10 studies that evaluated HIV seroconversion or seropositivity as outcomes 6 found that NSP use was protective [59-64]; outcomes in 2 studies were negatively associated with NSP use [65, 66] and 2 studies showed no effect [67, 68] (Tables 3a-c).

HIV risk behaviour outcomes were examined in 33 studies (with some authors reporting on more than one study or outcome). The majority focused on syringe sharing, borrowing, lending or reuse (23 positive [63, 69-90], 1 negative [91] and 5 indeterminate [92-96]), while 6 studies examined diverse outcomes including 'injection frequency' (1 positive) [73], 'proportion of syringes exchanged' (1 indeterminate) [97], 'syringe return rate or exchange rate' (3 positive) [98-100] and 'mortality among NSP users versus non-users' (1 indeterminate) [101] (Tables 4a-c).

Overall, these studies provide strong evidence to reject the null hypothesis that attendance at NSP does not confer protection against HIV. However, it is not possible to exclude the possibility that selection bias may account for the findings in studies comparing IDUs who attend NSPs with those who do not.

Several authors have offered explanations for the counterintuitive finding of some studies that HIV was more prevalent in attenders compared with non-attenders [67, 102-105]. It is well known that NSPs in many settings attract high-risk IDUs, who may therefore have a higher risk of HIV seroconversion before ever attending the programme. This self-selection factor may help explain why cities such as Montreal and Vancouver have observed higher HIV seroconversion rates among NSP attenders compared to non-attenders [67, 106].

As pointed out by Bastos et al. [103], evaluations of NSPs typically employ dichotomous categorizations (such as NSP attenders vs non-attenders, frequent vs infrequent attenders). This simplistic approach overlooks the fact that non-attenders may have only used sterile injecting equipment, obtaining these from sources other than NSPs. For example, in an analysis of NSP attenders in Amsterdam, a city where sterile syringes are readily available through pharmacies, irregular NSP attenders, but not non- or frequent attenders, were at highest risk of HIV seroconversion [96]. The authors concluded that irregular NSP attenders had the least exposure to sterile injection equipment and consistent prevention messages, which placed them at highest risk of infection.

Studies examining NSP effectiveness have generally relied on self-reported outcome measures. At least one study compared self-reported risk behaviour with actual programme data and concluded that self-reported risk behaviour data underestimated the protective association of NSP attendance by 18% [107].

Strong as the evidence is for NSP effectiveness, these data are confounded by the presence or absence of alternative availability of sterile injecting equipment through pharmacies. A systematic review [10] identified 42 published studies evaluating NSP effectiveness. The potential confounding of pharmacy access to syringes for these studies [89] was examined. There were 28 studies that concluded that NSP use had positive effects (reduced risk-behaviour or seroconversion), 12 showed no effectiveness and 2 found negative effects. Of the 14 studies with no effect or negative effects 13 compared clients with non-clients of NSPs. When these 13 studies were examined carefully and an additional 12 studies that compared

users with nonusers of NSPs were considered, all 13 studies with negative or null findings were found to have been conducted in settings where IDUs had legal access to syringes from pharmacies as well as NSPs. By way of contrast, in settings with NSPs but without additional legal access to sterile injecting equipment, there were no negative or null findings. Five studies found positive effects (reduced risk behaviour and/or seroconversion) despite legal access through NSPs and pharmacies. Nevertheless, the relationship between pharmacy access (yes/no) and positive vs negative findings was significant at the p=0.002 level. Finally, when studies in settings where legal pharmacy access was available were excluded, 23 of the remaining 24 studies showed positive effects for NSP use (Table 4d.).

There is sufficient evidence to consider that the criterion of 'strength of association' has been fulfilled.

3.2.2 Replication of findings

The above findings strongly support the effectiveness of NSPs as interventions that reduce risk behaviour such as syringe sharing among IDUs and HIV infection. The number of studies showing protective effects far outweighs those with ambiguous or negative effects. The preponderance of positive findings is strengthened by their replication by different authors, at different stages of the HIV epidemic, at different times and geographical locations and with diverse study designs. Furthermore, in instances where NSP use has been statistically associated with increased HIV incidence or higher-risk behaviours, convincing arguments for possible sources of confounding have been presented.

The efficacy of individual NSPs has been reported in at least 10 different countries, including several resource-poor countries. In addition, ecological studies have found strong associations between NSP implementation and lower HIV incidence and prevalence in comparisons involving diverse countries. Most notably, the Return on Investment study [64] compared HIV prevalence in 103 cities in 24 countries and 16 of these countries had NSPs. HIV seroprevalence was found to have declined by a mean annual 18.6% for 36 cities with NSPs compared to an 8.1% increase in 67 cities without NSPs. Hurley et al. [62] compared HIV seroprevalence among IDUs in 52 cities without NSPs and 29 cities with NSPs in Asia, Europe, North America, South America and the South Pacific. On average, seroprevalence increased by 5.9% per year in the 52 cities without NSPs and decreased by 5.8% per year in the 29 cities with NSPs.

In a recent systematic review, results favouring the efficacy of NSP use were recorded from six studies with longitudinal/prospective designs, four studies with multiple cross-sectional designs, eight observational studies, five ecological studies and several modelling studies [10].

There is sufficient evidence to consider that the criterion of 'replication of findings' has been fulfilled.

3.2.3 Specificity of association

Many studies have demonstrated multiple additional health benefits of NSPs apart from a reduction in HIV infection. These additional benefits include improved entry to primary health care and drug treatment, prevention of other blood-borne viral infections, reduced proximal bacterial infection (e.g. abscess and cellulitis) and reduced distal bacterial infection (e.g. subacute bacterial endocarditis, brain abscess). NSPs offer a 'package' of different services, including education about protection against other blood-borne viruses and sexually acquired HIV, education about cleaning injection equipment and information about drug treatment.

Reductions in risk behaviour and HIV seroconversion could be the result of these other services (such as acquiring clean syringes from pharmacies, using condoms and other safer sexual practices) rather than the needle and syringe exchange, distribution or sale. Although reduced HIV infection is not the only benefit of NSPs, the other benefits are less well documented and do not seem to be as powerful as the impact on HIV infection. There do not appear to be any well documented accounts of declining HIV incidence in a population with high prevalence levels in the absence of NSPs. Although the existence of these additional benefits is attractive from a public health and policy perspective, the effect of NSPs does not appear to be specific to HIV prevention.

There is sufficient evidence to consider that the criterion of 'specificity of association' has not been fulfilled.

3.2.4 Temporal sequence

While NSPs are not the only intervention credited with achieving reduced risk behaviour, in the large majority of settings where an NSP was introduced, a subsequent reduction in risk behaviour, and where measured, HIV seroconversion, has been reported.

As discussed above (3.2.1 Strength of association), in settings where NSP implementation has been followed by increased risk behaviour and/or seroconversion among actual NSP users, the availability of pharmacy access to clean syringes has been shown to confound study results [89]. NSP clients have also been shown at baseline in two studies to be at greater risk of HIV seroconversion than non-clients [67, 106]. It is now thought that the findings in these studies resulted from selection bias and other factors. A unique study in Windham, Connecticut observed "reversal" effects on risk behaviour among IDUs when an NSP was closed down. Significant increases in syringe reuse and syringe-sharing occurred post-closure compared with pre-closure [108]. Any resulting change in HIV infection rates was not measured. These observations are consistent with the expected direction of temporal sequence.

A number of studies measured behaviour at multiple points over time and all supported an appropriate temporal sequence. In New York City, 584 IDUs attending NSPs were interviewed on three occasions and HIV drug risk behaviour was found to decline with the continuing use of NSPs [109]. Heimer and colleagues, in their evaluation of the New Haven needle exchange, demonstrated that the prevalence of HIV in syringes decreased following an increase in the exchange rate [60]. In a large multiple cross-sectional study of 1304 untreated IDUs in Oakland, the United States, needle- and syringe-sharing declined over time concurrent with an increase in NSP use and distribution of supplies [85].

Analysis of trends in HIV risk behaviours among over 5000 IDUs in New York City from 1990 to 1997 led to the conclusion that all three injection risk behaviours studied declined significantly (all $p<0.01$) accompanied by a substantial increase in syringe exchange participation. Seroprevalence among IDUs also declined from about 45% in 1991 to about 30% in 1996 [110]. There do not appear to be any published studies reporting an unexpected temporal sequence.

There is sufficient evidence to consider that the criterion of 'temporal sequence' has been fulfilled.

3.2.5 Biological plausibility

Although the minimum quantity (infectious dose) of HIV necessary to result in infection is not known, viable HIV has been detected in syringes stored at room temperature for up to four weeks [27]. Field studies confirm that HIV can be detected in blood contaminated syringes for some weeks. The presence of HIV-1 RNA in needles and syringes indicates the risk associated with sharing of needles and syringes, and presumably also paraphernalia and wash waters by IDUs. A study of needles and syringes obtained from shooting galleries in Miami found that 39% of rinses from 36 needles and syringes containing visible blood had detectable amounts of HIV-1 RNA when quantified and analysed for the presence of antibodies for viral proteins. Antibodies to HIV-1 polypeptides were detected in 94% of the same sample [25]. Earlier studies found HIV-1 in 3% of blood-contaminated needle and syringes collected from exchange programmes in Sydney [26], 10% of needle and syringes from shooting galleries in South Florida [24], 50% of used needles and syringes obtained from shooting galleries in Miami [21, 111, 112] and in New Haven, Connecticut HIV-1 was detected in 67.5% of used "street" syringes and in 91.7% of needles from a shooting gallery [60].

Further evidence of a biologically plausible link between the use of shared injecting equipment and HIV seroconversion among IDUs is provided by field studies of the biological mechanisms of HIV transmission among IDUs. Practices such as registering, "booting" and "backloading" have been shown to increase the risk of HIV-1 transmission by directly placing blood within the needle and syringe [113-115]. Chitwood et al. used logistic regression analysis that adjusted for age, gender and race to determine risk factors associated with HIV-1 seroconversion among IDUs. They found that sharing needles and syringes in the year prior to conversion was the primary independent risk factor and it was much stronger than sexual factors [116]. Other studies have broadened the definition of sharing to shared injection paraphernalia such as cookers, cottons and rinse water and to the practice of "frontloading".

IDUs with a history of diabetes have a significantly lower HIV seroprevalence rate (9.8%) compared with non-diabetic IDUs (24.3%) ($p=0.03$). This result highlighted that increased access to sterile syringes and less use of contaminated equipment were important factors contributing to lower HIV infection rates [117].

One study investigated where IDUs obtain needles and syringes from prior to the implementation of NSPs. A cross-sectional study of 741 current IDUs in

Baltimore found that most (85%) participants obtained at least some needles from street needle sellers [118]. Participants who sold needles reported that it was easy to make used needles appear to be unused, and some admitted to selling used syringes as new. The authors concluded that street needle sellers were an important source of needles for drug injectors, and few injectors were able to determine whether these needles were actually sterile.

There is sufficient evidence to consider that the criterion of 'biological plausibility' has been fulfilled.

3.2.6 Biological gradient

Heimer et al. [60] found in their syringe tracking study in New Haven that HIV prevalence in syringes decreased as the exchange rate increased. Few studies have investigated a possible relationship between increased implementation of NSPs and reduced HIV infections.

There is insufficient evidence to consider that the criterion of 'biological gradient' has been fulfilled.

3.2.7 Coherence of the evidence

The arguments for coherence of the evidence span several of the Bradford Hill criteria, including biological plausibility, strength of association and replication. To minimize repetition, material that has already been presented will not be repeated in this section.

There is strong evidence that HIV can be transmitted when contaminated injection equipment is shared and such sharing is the strongest risk factor predicting HIV seroconversion among IDUs. Studies of IDU risk behaviour in settings without NSPs show that most engaged in needle-sharing and other unsafe injecting practices. For example, in a cross-sectional survey of active IDUs in Baltimore, Maryland almost 50% of respondents said their usual source for needles and syringes was street dealers and a further 4.1% said their usual source was "friends/neighbours" or "shooting galleries" [119]. A number of studies investigating the main risk factors for HIV seroconversion found syringe-borrowing to be an independent determinant [120] while some studies also found that "backloading" and "frontloading" were independent predictors.

Modelling studies have demonstrated that obtaining clean needles from NSPs reduces the circulation time of each syringe, whether for reuse by the same IDU or for sharing with other IDUs. Evaluations of numerous NSPs in many countries have concluded that IDUs who attend NSPs reduce their HIV risk behaviours compared with those who do not attend, and that the evidence is particularly consistent in areas where non-attenders cannot obtain clean needles from any other sources (such as pharmacies or vending machines). Even in areas where pharmacy and other access to sterile syringes is available, the large majority of studies show that NSP use is significantly associated with a decline in risk behaviour [89].

Evidence that a reversal to the status quo occurs after an intervention is withdrawn adds further to the coherence of arguments for causality. The positive effects of NSPs were observed when a needle exchange in Windham, Connecticut was closed. A significantly higher percentage of former exchange users reported obtaining syringes from an unreliable source and syringe sharing more than doubled, compared to pre-closure [108]. Some large ecological studies show a clear association with NSP implementation and declining HIV incidence and prevalence over time.

Evidence for the efficacy of NSPs in stemming the spread of HIV has been questioned because of an apparent lack of effect for HCV. HIV entered drug injecting populations in New York during the mid-1970s and Australia in the early 1980s while prevention measures such as NSPs only began to be established in the early 1980s. In contrast, hepatitis C first spread among IDUs in the 1960s and therefore had a comparatively higher baseline prevalence by the time NSPs were instigated [121]. Hepatitis C is about an order of magnitude more infectious by blood-blood contact than HIV [121, 122]. Despite some reported disparities there is increasing evidence that use of syringe exchanges has led to significant reductions in both hepatitis B and C [123].

There is sufficient evidence to consider that the criterion of 'coherence of the evidence' has been fulfilled.

3.2.8 Experimental evidence

An appropriate experiment could theoretically be provided by an RCT whereby IDUs were randomly allocated to an experimental group who would be issued with an adequate supply of sterile syringes at an exchange and a control group who would not be provided with sterile syringes. The experiment

would need to take place in a setting isolated from potential access (by controls) to pharmacy or vending machine syringe acquisition. Other possible confounding factors would need to be measured and controlled for such as rate of incarceration, availability and quality of drug treatment (especially methadone treatment for heroin dependence), utilization of strategies to reduce sexual transmission (such as condoms and treatment of sexually transmitted infections) and overlap with "bridge" populations (men who have sex with men and commercial sex workers). As already discussed, there are strong logistical and ethical arguments against conducting such experiments.

There is insufficient evidence to consider that the criterion of 'experimental evidence' has been fulfilled.

3.2.9 Reasoning by analogy

The provision of sterile injecting equipment to reduce HIV infection among IDUs has many similarities with condom provision to reduce sexual transmission of HIV. These interventions both have high biological plausibility. Condom provision is well accepted to have strong support from empirical evidence of effectiveness [124]. It could be argued that both are implemented less vigorously than would be justified by the evidence of effectiveness, safety and cost-effectiveness. Concern has often been expressed that condom provision might inadvertently increase unsanctioned sexual activity such as reducing the age of initiation, and increasing the frequency of sexual activity, especially among unmarried partners. There is no convincing evidence to support these concerns despite numerous and diligent attempts to detect these or other unintended negative consequences [124]. Drug use and sexual activity are sensitive issues in virtually all countries, especially when these occur among teenagers. Like NSPs, condom provision has considerable benefits apart from reduction of HIV infection, such as reducing the incidence of sexually transmitted infections and unwanted pregnancies. Condom provision and NSPs are both cost-effective interventions.

There is sufficient evidence to consider that the criterion of 'reasoning by analogy' has been fulfilled.

3.2.10 Cost-effectiveness

Many studies have demonstrated that the implementation of NSP is cost-effective and cost-saving. In a retrospective analysis, Lurie & Drucker estimated that the number of HIV infections that could have been prevented in the United States had NSPs been implemented during the early stages of the HIV/AIDS epidemic was between 4394 (with a 15% incidence reduction due to NSPs) and 9666 (with a 33% incidence reduction). The cost to the United States health care system of treating these HIV infections was calculated at between US$ 244 million and US$ 538 million respectively [102].

Furthermore, Lurie et al. also estimated the cost per syringe distributed for five syringe distribution strategies (a NSP, a pharmacy-based NSP, free pharmacy distribution of pharmacy kits, sale of such pharmacy kits to IDUs and sale of syringes in pharmacies) [125]. All five strategies could distribute syringes at relatively low unit cost, with NSPs being the most expensive and syringe sales the cheapest. At an annual seroincidence exceeding 2.1% all strategies were estimated to be cost saving.

Others have used mathematical modelling to estimate the cost per HIV infection averted by NSPs. Holtgrave et al. estimated that 100% coverage of a previously unmet need for sterile syringes for IDUs in the United States would require 954.8 million syringes at a cost of US$ 423 million. This would prevent 12 350 cases of HIV, with subsequent HIV treatment costing approximately US$ 1.3 billion [126]. Total societal expenditure of US$ 277 million was estimated for NSP costs with US$ 145.8 million for pharmacy-based sales. It was estimated that one third of the cost would comprise out-of-pocket payments by IDUs purchasing syringes from pharmacies. This amounts to a cost saving of US$ 34 278 per HIV infection averted, well under the estimated lifetime medical costs of treating an HIV infected individual (US$ 108 469).

Using conservative estimates, it was predicted that the Hamilton NSP in Canada [127] would prevent 24 cases of HIV infection over five years, thereby providing cost savings of US$ 1.3 million after the programme expenses were taken into account. This translates into a savings cost ratio of 4:1.

The cost-effectiveness of the Edmonton Streetworks NSP in Canada was estimated at CAD$ 9500 per HIV infection delayed for one year [128]. The discounted cost per case averted was less than the cost of a case of AIDS.

A variety of HIV prevention strategies was compared for cost-effectiveness in an east coast city of the United States. Cost per HIV infection prevented was lowest for needle exchange and counselling/education (about US$ 4000) [129].

The cost per HIV infection averted for a year by an NSP in New York City was estimated to be US$ 2667. This is far below the estimated cost of lifetime medical treatment for one HIV-infected individual (prior to protease inhibitors)—US$ 56 000 to US$ 80 000. Thus, the net cost savings per HIV infection averted for an NSP in New York City could be estimated to be US$ 53 000 to US$ 77 000 [130].

Another analysis of New York State-approved NSPs concluded that syringe exchange is a cost-effective and cost-saving strategy for reducing HIV transmission [131] with an estimated 87 HIV infections averted across seven programmes at a total cost of US$ 1.8 million, resulting in a cost-effectiveness ratio of almost US$ 20 947 per HIV infection averted.

A cost-effectiveness study of NSPs in Svetlogorsk, Belarus evaluated a comprehensive strategy that included NSPs, safe sex counselling, condom promotion, bleach distribution and referral for STD services. The average cost per HIV infection averted was estimated at only US$ 68 (estimated range: US$ 54 to US$ 100) [132]. If the cost of the associated mass-media campaign is included, the cost per HIV infection averted rises to a range of US$ 240 to US$ 442, still notably cost-effective. This is a very significant study because it confirms that the cost-effectiveness of NSPs as an HIV prevention measure also applies in a resource-poor setting.

A cost-effectiveness study assessed whether prevention interventions targeted at high-risk populations have a greater effect on the number of HIV infections prevented than if they are targeted to low-risk populations. Assuming that the programme reduces risk behaviours by a modest 10%, the study showed that US$ 1 million in annual prevention spending over five years could prevent about 100 HIV infections in high-risk populations with HIV prevalences of 10-15% (such as IDUs) [133]. The same study also highlights the fact that there are certain cases where a simple cost-effectiveness analysis does not reflect the value of a programme. For example, some programmes benefit more risk groups than just their audience.

A cost effectiveness analysis applied a simplified Yale Needle Circulation Model to four hypothetical NSPs in four United States cities with differing HIV prevalence and incidence rates. Reductions in HIV incidence rates varied across cities from 17% to 70% across the four hypothetical settings. Higher reductions were associated with more needles per client-year and greater efficiency was associated with low cost per needle exchanged. The estimated cost savings per HIV infection averted ranged from US$ 12 000 to US$ 99 000 [134].

Most cost effectiveness studies have been conducted in developed countries, with far fewer conducted in resource-poor settings.

There is sufficient evidence to consider that the criterion of 'cost effectiveness' has been fulfilled.

3.2.11 Absence of negative consequences

Studies have searched for and found no convincing evidence of the following unintended complications associated with NSPs: greater injection frequency [69, 73], increased illicit drug use [135, 136], a rise in syringe-lending to other IDUs [67, 69], recruitment of new IDUs [60, 73, 137], social network formation [138], greater numbers of discarded used needles [108, 139, 140], less motivation to change, i.e. reduce, drug use [141] and increased transition from non-injecting drug use to IDU [136].

There is sufficient evidence to consider that the criterion of 'absence of negative consequences' has been fulfilled.

3.2.12 Feasibility of implementation, expansion and coverage

The implementation of NSPs has been shown to be successful in a variety of settings. The historical development of NSPs in Germany has been described, concluding that establishing programmes in larger cities was easier than meeting demand in smaller cities and more conservative states. Establishing NSPs in German prisons was considered desirable but only possible as pilot projects on a limited basis [142]. An ecological study of IDUs in seven United States metropolitan areas demonstrated that the IDUs were more likely to have used a reliable source for obtaining their most recent syringe in cities with a NSP (OR=5.3; 95% CI 3.3-8.5) [84].

NSPs have been successfully established in a few resource-poor settings, such as Hanoi in Viet Nam [143], Kathmandu in Nepal [77], and northern Thailand [144]. A report on NSPs in northern Thailand mentioned cooperation from government agencies and

nongovernment agencies in addition to the local communities as key factors for successful implementation [144]. The Hanoi NSP gained local acceptance by holding workshops with key community people, including the local police, using outreach services to distribute needles and syringes rather than at established exchange sites, using appropriate methods to collect used injection equipment, and by training and recruitment of ex-user outreach workers [143].

Successful implementation has also been achieved in some transitional countries such as Svetlogorsk, Belarus (eastern Europe) [132] [145] and Sverdlovsk Oblast, Russia [88]. The latter was achieved through a process of "many months of negotiation and discussion with all relevant agencies" including the Ministry for Internal Affairs, (which is responsible for law enforcement). These processes also encompassed educating officials at seminars at which international research evidence of best practice was presented, a study tour to visit harm reduction programmes in Britain and a series of training workshops for workers at the pilot sites. It was necessary to provide an early evaluation report to satisfy politicians and health-care providers so that the project could continue. A number of international organizations were also involved to encourage policy-makers and health practitioners to implement harm-reduction strategies, and in particular to champion NSPs [88].

An evaluation of a Hawaiian NSP showed that the following characteristics were required to achieve sustainable high coverage: broad-based political support; allocation of public funds; progressive expansion and removal of counter-productive aspects; peer-educators; links to other services for drug users, especially drug treatment; and periodic formal evaluation [146].

It is noteworthy that implementation of NSP in the early stages of an HIV epidemic (when seroprevalence is still low), combined with multiple prevention initiatives including community outreach, has been shown to have maximum impact [147].

Early and vigorous implementation has been demonstrated in a number of countries. The first NSP was established in Australia in 1986 and within a couple of years, a national network of programmes had been implemented with a throughput of 30 million needles and syringes in 2000 for a population of less than 20 million [64]. However, in many countries implementation has been delayed and the scale has been inadequate. This is especially true in developing and transitional countries, or countries that respond to illicit drugs with a predominantly supply control perspective [103].

There is sufficient evidence to consider that the criterion of 'feasibility of implementation, expansion and coverage' has been fulfilled.

3.2.13 Unanticipated benefits

A number of studies have demonstrated additional benefits resulting from NSP use, apart from a reduction in injecting risk behaviour and HIV infection. At the New Haven and Seattle exchanges, increased enrolment in drug treatment was reported as well as higher treatment retention rates compared with non-users of NSPs [148-150]. An evaluation study in Baltimore found that NSP attendance was independently associated with entry into drug treatment for HIV-infected IDUs [151]. In San Francisco, Bluthenthal [86] found that NSP clients attitudes and motivation to change their drug-using patterns was positive, and concluded that NSP is a possible link to drug treatment [141].

Gibson found NSP use to be associated with substantially reduced injecting or cessation of injecting compared to IDUs who had never attended an NSP [150].

During a pilot NSP conducted in a Swiss women's prison for a year, no injection abscesses were observed and there were no instances of aggressive or threatening behaviour among inmates using syringes [31].

There is sufficient evidence to consider that the criterion of 'unanticipated benefits' has been fulfilled.

3.2.14 Special populations

Prisons:

A pilot intervention project was carried out in a Bern prison accommodating up to 110 women, of whom a high proportion injected drugs while imprisoned. Sterile injection equipment was made available from a one-to-one automatic dispenser. Before distribution of injection material, nearly half of the prisoners who injected drugs reported sharing injecting material regularly, whereas sharing virtually ceased during the experiment. A total of 5335 syringes were exchanged during the project (0.2 syringes/day per inmate) [31].

Mathematical modelling has been proposed as a useful technique for estimating HIV transmission in

prisons [57]. Using conservative assumptions, where measurement of relevant variables for the model was unavailable, a relatively large number of HIV infections were estimated to occur in prisons through sharing of injection equipment. Importantly, these observations were made even in a country where HIV prevalence among IDUs is low.

By December 2000, 19 prisons in 3 countries had syringe exchange programmes. All evaluations of these programmes have been favourable and without reported unintended negative consequences [152].

Young IDUs:
Young IDUs have been found to be at higher risk of acquiring HIV. Multivariate analysis in one study showed recent onset injecting to be an independent predictor for seroconversion [153]. A study of IDUs in Rio de Janeiro, Brazil found that younger age was the principal factor associated with high injecting risk behaviour [154]. In most countries, young people appear to be under-represented among IDUs attending NSPs. This may be because attendance at an NSP amounts to a relatively public identification as an IDU.

A study which investigated an HIV prevention programme for homeless young adult IDUs in San Francisco, United States found significant differences between IDUs who frequented a secondary NSP intervention site and a comparison group who did not [155]. The comparison group were more at risk of sharing syringes (AOR = 3.748;95% CI, 1.406-9.988) and reusing syringes (AOR = 2.769; 95% CI, 1.120-6.847).

"Bridge" populations
Several studies have observed that women who attend NSPs and engage in sex work typically report greater HIV risk than women non-sex workers attending NSPs. A study comparing sex workers with non-sex workers in five United States cities found that sex workers were significantly more likely to inject more frequently ($P<0.0005$), to reuse syringes more than twice ($P<0.005$), to engage in "backloading" syringes ($P<0.005$) and to obtain syringes from non-NSP sources ($P<0.05$) [156]. Current sex workers in a Vancouver study engaged in heavier drug use, reported a greater variety of injection and non-injection drugs and injected substantially more frequently than both sexually active and non-sexually active women [67]. They also engaged more frequently in risky injection practices, such as renting, buying or borrowing used syringes and using shooting galleries than other women. Extensive HIV infection has occurred among commercial sex workers in some countries before a generalized epidemic, e.g. Thailand [157, 158].
IDU men who have sex with men constitute another "bridge" population. A Brazilian study that aimed to determine risk factors for HIV-1 among IDUs (n=123) in Rio de Janiero found that being a male who has had sex with men in the previous five years was a significant independent risk factor for HIV infection. The authors concluded that homosexual/bisexual male drug injectors may have been a "bridge" group through which HIV entered drug-injecting networks in that city [159].

Developing countries
Successful NSP interventions have been set up either as pilot programmes or ongoing services in a number of developing countries, including three remote villages in northern Thailand [144], Hanoi, Viet Nam [143] and Dhaka and Rajshahi, Bangladesh [160]. Evaluation results for these studies were reported above under 'Strength of association' and they were further discussed under 'Feasibility of implementation, expansion and coverage'.

There is sufficient evidence to consider that the criterion of 'special populations' has been fulfilled.

3.3 The effectiveness of the sale of needles and syringes from pharmacies and vending machines in preventing HIV infection among injecting drug users

3.3.1 Strength of association

Nine studies were identified that examined the effect of pharmacy sales and syringe vending machines in reducing a number of risk behaviour outcomes (including less syringe borrowing, sharing and injecting, never borrowing injecting equipment and less syringe re-use) and HIV seroprevalence among IDUs [117, 119, 161-167] (Table 5).

Access to sterile needles and syringes from community pharmacies and syringe vending machines was shown in all nine studies to be effective in reducing risk behaviour and HIV seroprevalence. Evaluation results were also positive and significant in locations

where there were no syringe exchange programmes available [167, 168]. In Hong Kong Special Administrative Region (Hong Kong SAR), no prescription is required to purchase syringes at pharmacies and there is a network of methadone clinics that has been well established since the 1970s. Health department reports show that only 2% (12/602) of cases with HIV infection are attributable to IDUs with a history of needle-sharing. HIV prevalence of less than 1% has been reported consistently in a number of community surveys [168].

Some countries have sought to increase the availability of sterile syringes by installing vending machines that sell or exchange syringes. This strategy can provide 24-hour availability and improve access in locations that are difficult to service. A study in Berlin found that 77% of IDUs used vending machines regularly (> 4 times a week) [169]. In Marseille, France it was reported that 21.3% of IDUs used vending machines as a primary source of syringes [165]. Primary users of vending machines were less likely to be HIV positive (OR 0.5; 95% CI 0.2, 0.9) but this was not significant after adjustment [165]. The introduction of vending machines in an open prison for males in Hamburg, Germany resulted in significant decrease in needle-sharing and no new individuals with HIV infection were identified during the programme [166].

No indeterminate or negative studies were identified for either pharmacy sales or vending machines.

There is sufficient evidence to consider that the criterion of 'strength of association' has been fulfilled.

3.3.2 Replication of findings

Pharmacy and vending machine access to sterile needle syringes among IDUs has been evaluated in a number of countries including Australia, Canada, France, Germany and the United States, each with different HIV prevalence rates in IDU populations and with different settings. Study setting (legislative environment) influenced the availability and access to sterile needles and syringes with no legal restrictions on the sale and possession of sterile injecting equipment in most settings. In these areas, positive results were consistent.

In a systematic review of studies evaluating cities with low HIV seroprevalence among IDUs (less than 5% over five years) Des Jarlais and colleagues found that one of the common characteristics was legal pharmacy sale as a source of sterile injecting equipment [147].

A study carried out in Georgia in 1998 attributed a low HIV infection rate, despite high prevalence of injecting drug use, to the ready availability of syringes in pharmacies and the lack of social stigma associated with injecting drug use [170].

There is sufficient evidence to consider that the criterion of 'replication of findings' has been fulfilled.

3.3.3 Specificity

Several outcomes (including reduced needle-sharing, borrowing and sharing of drug-injecting equipment) have been identified as a direct result of increased sales of sterile needles and syringes from pharmacies and vending machines.

However, a study in Vancouver by Strathdee et al. highlighted the importance of deregulation of syringe sales in pharmacies in order to increase access to sterile injection equipment and thereby maintain low HIV seroprevalence [66]. HIV prevalence in Vancouver during 1996 was reported to have increased to 23.2% and this was attributed to a number of factors including IDUs having inadequate access to drug and alcohol treatment, methadone maintenance and counselling services. The authors note that without adequate and appropriate community-wide interventions such as addictions treatment, detoxification and counselling services, stand-alone measures to increase access to sterile injection equipment appear to be a necessary but not a sufficient factor in reducing risk-taking behaviour and maintaining low HIV seroprevalence [66]. These and other data support the value of the intervention. However, there is inadequate data to conclude that the outcome benefits are specific to HIV.

There is insufficient evidence to consider that the criterion of 'specificity' has been fulfilled.

3.3.4 Temporal sequence

On the basis of available evidence, increased pharmacy sales and availability of vending machines occurred first and changes in risk behaviour followed. A survey of more than 2000 IDUs in London in the United Kingdom between 1990 and 1993 found that HIV prevalence among IDUs declined from 12.8% to 6.9%. This coincided with increased availability of sterile syringes in pharmacies and needle exchange programmes (NEPs) after 1987 [163].

A prospective surveillance study performed before and after introducing the legal sale of sterile syringes in pharmacies in Connecticut in the United States (in July 1992) found a significant increase in pharmacy syringe sales [171]. Over the same period there was a decrease in syringe-sharing in the past 30 days (21%), a decline in obtaining syringes from the streets (14%), and fewer IDUs reporting ever having shared syringes (43% fewer) [164].
Prior to the liberalization of the sale of syringes in France in 1987, syringe sharing was reportedly routine practice among IDU due to the scarcity of syringes. Post-liberalization, the purchase of syringes at pharmacies increased such that over half (52%) of IDUs recruited from the streets in France and 40% undergoing treatment only used syringes they purchased and never shared with others [161].

There is sufficient evidence to consider that the criterion of 'temporal sequence' has been fulfilled.

3.3.5 Biological plausibility

The biological basis of reducing HIV infection by increasing access to sterile syringes through pharmacy sales and vending machines has been discussed in section 3.1.5.

There is sufficient evidence to consider that the criterion of 'biological plausibility' has been fulfilled.

3.3.6 Biological gradient

Increasing participation and sales by pharmacies of sterile syringes led to a corresponding decrease in risk behaviour [162, 164, 172]. This is consistent with a biological gradient but unless supported by additional evidence, cannot be considered to constitute sufficient evidence.

There is insufficient evidence to consider that the criterion of 'biological gradient' has been fulfilled.

3.3.7 Coherence of the evidence

As discussed above, the arguments in favour of pharmacy sales and vending machines span several criteria and are impressively consistent. However, the quantity of data is far less impressive than evaluation of NSPs.

There is sufficient evidence to consider that the criterion of 'coherence of the evidence' has been fulfilled.

3.3.8 Experimental evidence

There is no experimental evidence (such as an RCT to) support the efficacy of pharmacy sales and vending machine availability of sterile syringes. As discussed elsewhere, RCT evaluation of pharmacy sales and vending machine availability of sterile syringes is not feasible logistically and is generally considered to be unethical. Many public health interventions have not been evaluated by RCT for similar reasons and have nevertheless been fully accepted as effective and safe.

There is insufficient evidence to consider that the criterion of 'experimental evidence' has been fulfilled.

3.3.9 Reasoning by analogy

In many countries before the HIV/AIDS epidemic, condoms were only available from pharmacies following a specific request from a customer. When the magnitude of potential health, social and economic costs of uncontrolled HIV infection began to be better appreciated, condom availability was increased in many parts of the world. In most developed countries these days, condoms are now readily available from a wide variety of outlets, including pharmacies, supermarkets and vending machines. As with availability of sterile needles and syringes, once the principle that increased utilization of sterile injecting equipment and condoms is accepted and programmes to achieve this are implemented, evaluations of novel methods to further increase utilization are exceedingly difficult to undertake. We were unable to find evidence supporting a decline in sexual risk behaviours in connection with increasing "industrial" supply of condoms.

There is sufficient evidence to consider that the criterion of 'reasoning by analogy' has been fulfilled.

3.3.10 Cost effectiveness

A cost-effectiveness study by Lurie et al. [125] of five different pharmacy-based syringe distribution strategies (Section 3.2.10) found that the cost per syringe distributed ranged from US$ 0.15 for syringe sales to US$ 0.97 for NSP [125]. At an estimated cost of treating an HIV-infected person in a lifetime of US$ 55 640, it was estimated that if annual HIV seroincidence for IDUs is greater than 2.1% then all strategies will be cost saving to society. The syringe sale option would be cost saving if HIV seroincidence for IDUs is greater than 0.3%.

The costs and cost-effectiveness of a policy of increased availability of sterile syringes that would include NSPs (25%) and pharmacy sale of syringes (75%) [126] were estimated based on 1996 prices and populations in the United States. The total cost of complete coverage (100%) of providing sterile syringes to IDUs was approximately US$ 423 million. This was estimated to avert 12 350 new HIV infections in one year with a gross societal cost of over US$ 1339 million, representing a net saving of over US$ 916 million. Thus, the economic benefits are substantial and far greater than the costs. Hence, funding would save society long-term costs.

There is sufficient evidence to consider that the criterion of 'cost effectiveness' has been fulfilled.

3.3.11 Absence of negative consequences

Some pharmacists have expressed concern about the possibility of a negative impact of pharmacy sales of sterile syringes on pharmacy business and increased robberies or shoplifting. However, fewer than 20% have experienced these negative effects [171, 172].

In the United States, barriers to pharmacy sales have been removed without concurrent relaxation of strictly enforced drug paraphernalia laws, which raises concern about a possible increase in arrests and fines of IDUs.

No evidence was identified that increased pharmacy sales or the installation of vending machines have caused non-IDUs to become users.

There is sufficient evidence to consider that the criterion of 'absence of negative consequences' has been fulfilled.

3.3.12 Feasibility of implementation, expansion and coverage

Pharmacy sale of sterile needles and syringes without a medical prescription is permitted in many developed and developing countries.

In New South Wales, Australia [173] and Connecticut, the United States [171] legal access to the sale and possession of sterile needles and syringes was increased with a subsequent significant increase in sales and greater willingness of pharmacists to sell or supply sterile injecting equipment to suspected IDUs. Between 58% and 75% of pharmacists in locations where sale and possession of syringes is not prohibited said they were willing to sell syringes without a prescription [171-176] compared with 16%-23% of pharmacists working in areas where it is illegal to possess drug-injecting equipment [177, 178]. Increased pharmacy sales in the United Kingdom, Connecticut and in New South Wales have also been followed by a corresponding increase in the use of sterile injecting equipment by IDUs [172-174].

There is sufficient evidence to consider that the criterion of 'feasibility of implementation, expansion and coverage' has been fulfilled.

3.3.13 Unanticipated benefits

From a public health perspective, improved access to sterile needles and syringes from pharmacies and vending machines is likely to reduce other blood borne viral infections such as Hepatitis B and C. However, no papers specifically evaluating pharmacies and vending machines from this perspective were identified.

There is insufficient evidence to consider that the criterion of 'unanticipated benefits' has been fulfilled.

3.3.14 Special populations

Even in locations where it is legal for pharmacies to sell needles and syringes without prescription, pharmacists may still refuse to sell at their discretion [179]. Biases have been found in some studies against IDUs who were younger or from racial minorities and these provided barriers to access to sterile injecting equipment [175]. Interviews with 108 IDUs from Houston, Texas in 2000 revealed significant differences between IDUs from different ethnic groups with 0% (0/15) of African-Americans, 26% of Anglo-Americans and 35% of Hispanics purchasing syringes from pharmacies [167].

The introduction of vending machines in an open prison for males in Hamburg, Germany resulted in a significant decrease in needle-sharing. No new HIV infections were identified during the programme [166].

In a study in France in 1997, primary users of vending machines were more likely to be younger (<30 years) (AOR 1.3; 95%CI 1.1, 1.8); less likely to have lived in a house they personally owned or rented (AOR 0.7; 95%CI 0.5, 0.9); less likely to have been in drug maintenance treatment (AOR 0.7; 95%CI 0.5, 0.9) and less likely to have shared needles or injection equipment (AOR 0.5; 95%CI 0.4, 0.8) [165].

There is sufficient evidence to consider that the criterion of 'special populations' has been fulfilled.

3.4 Evidence for needle syringe disposal

3.4.1 Summary of papers of disposal of needles and syringes

The few papers published on disposal of used needles and syringes do not allow evaluation of the diverse strategies adopted in various countries according to the Bradford Hill criteria (Table 6). In many countries, NSPs and other outlets for sterile injection equipment are vulnerable to public criticism. Widespread disposal of used injection equipment in public places undermines the political sustainability of sensitive needle syringe and pharmacy programmes. For example, an NSP was closed in Windham, Connecticut in May 1997 following public controversy in which it was blamed, among other things for discarded syringes. However, post-closure surveys of outdoor drug-use areas found that the closure of the exchange did not in fact reduce the volume of discarded syringes and other drug-injecting debris [108].

The papers identified show that diverse measures have been adopted to improve disposal practices and some have met with approval by a wide variety of groups. There are no published reports thus far that indicate that used injection equipment discarded in a public place has led to infection with a blood-borne virus (personal communication Dr Andrian Reynolds). Criminal penalties for possessing needles and syringes may have the inadvertent effect of deterring IDUs from disposing of used injection equipment responsibly.

There is insufficient evidence to consider that any of the Bradford Hill and additional criteria for needle syringe disposal have been fulfilled.

3.5 Injecting paraphernalia legislation

Before the global HIV/AIDS pandemic was first recognized, a variety of legislative approaches existed for injecting equipment. In some countries, there were no legislative barriers to the sale of sterile injecting equipment. In other countries, legislation specifically prohibited provision of used injecting equipment to IDUs. The United States had among the most severe restrictions with some states prohibiting possession of injecting equipment and others requiring a doctor's prescription for purchase of sterile injecting equipment. Virtually all publications regarding injecting paraphernalia legislation originate from just one country (the United States) and may not be generalizable to other countries. However, for the purposes of this review it has been assumed that these findings are more widely generalizable. The null hypothesis considered in this section is that injection paraphernalia legislation that restricts sterile needle and syringe availability does not reduce HIV infection.

3.5.1 Strength of association

There is a significant positive correlation between legal restrictions on syringe access and HIV seroincidence and seroprevalence [61, 180]. HIV infection among IDUs is more likely to occur in legal environments where sterile injection equipment is more severely restricted. However, these findings may be subject to confounders, measurement error (HIV seroincidence and seroprevalence), and recall bias (legal restrictions on syringe access).

In jurisdictions in the United States, where drug paraphernalia laws were strictly enforced, higher prevalence of HIV infection was observed despite lower risk-taking behaviour. Legal barriers in Maryland and Texas in the United States resulted in a high prevalence of HIV with up to 25% of IDUs infected in Baltimore, Maryland [119] and 35% of IDUs infected in Houston, Texas [167]. These findings overall suggest that injecting paraphernalia legislation that restricts needle and syringe availability inadvertently increases HIV infection. There is no convincing evidence that this legislation reduces HIV prevalence.

There is insufficient evidence to consider that the criterion 'strength of association' has been fulfilled.

3.5.2 Replication of results

The two studies [61, 180] evaluating the impact of injecting paraphernalia legislation only reported data from one country (the United States) and thus may not be generalizable to other countries. While these papers used different methods (meta-analysis and cross-sectional ethnography), both types of studies concluded that HIV infection was significantly more

common in areas with restrictive legislation than in areas where NSPs could operate legally and/or there was no legislative restriction on the purchase or sale of syringes.
The impact of restrictive legislation has also been assessed on secondary outcomes such as IDU's behaviour and NSP or pharmacy provision of sterile syringes [84, 171]. These were retrospective ecological studies of IDU self-reported behaviour, NSP directors' reports, and pharmacists' beliefs. One study included a prospective sampling of pharmacists' actions after the repeal of prescription laws [171]. Replication of findings is hard to assess due to the limited number of papers assessing the same outcome variables. However, removal of legislation appears to have had a positive impact on the operation of NSPs and increased the availability of sterile syringes. Additionally, the simultaneous repeal of prescription and possession laws seems to have a greater effect than repeal of only one of these [84].

These findings suggest that, overall, injecting paraphernalia legislation that restricts needle and syringe availability inadvertently increases HIV infection, while there is no convincing evidence that this legislation reduces HIV infection.

There is insufficient evidence to consider that the criterion 'replication of results' has been fulfilled.

3.5.3 Specificity

HIV incidence is influenced by multiple factors apart from legislation, including the existence of legal and illegal NSPs, drug treatment and the numerous other factors that influence the sexual transmission of HIV (such as the prevalence of sexually transmitted infections, the rate of sexual partner change). In some cities where sterile needles and syringes are readily available, HIV epidemics appear to have been averted [62]. It is much easier to evaluate the effectiveness of needle syringe programmes than legislation because programmes have a more direct impact on benefits and side effects whereas legislation has a relatively indirect influence. When legislation creates an enabling environment, programme activity may still be delayed or perfunctory in scope. In contrast, restrictive legislation banning needle syringe programmes is sometimes ignored with sizeable unsanctioned programmes established, albeit with some difficulty.

In the two studies relating HIV outcomes and legislation [61, 180], there was no randomization of study participants or geographical areas and therefore conditions other than a change in the law may have reduced the use of sterile syringes and HIV seroconversion. The authors of these papers identified no other benefits or disadvantages of injecting paraphernalia legislation.

As discussed elsewhere in this report, extensive evidence is available to reject the null hypothesis that providing sterile needles and syringes does not prevent the transmission of HIV. Legislation and law enforcement are major factors limiting the supply of and access to sterile syringes [181]. Despite the limited number of studies evaluating the impact of legislation on IDU access to sterile syringes and HIV incidence and prevalence, it is reasonable to conclude that restrictive legislation reduces access to sterile needles and syringes, thereby increasing HIV transmission. Therefore, there is inadequate data to establish that injecting paraphernalia legislation specifically effects HIV (as opposed to other micro-organisms).

There is insufficient evidence to consider that the criterion 'specificity' has been fulfilled.

3.5.4 Temporal sequence

Neither study of HIV outcomes [61, 180] evaluated a possible temporal sequence.

Temporal relationships were studied in an assessment of risk behaviours immediately after a change in legislation. Following legislative changes, purchase of syringes from a pharmacy increased and syringe sharing and reported street-purchase of syringes decreased [164]. In a second study in several cities in Connecticut in the United States with a high prevalence of HIV among IDUs, legislative change was followed by an increase in the number of syringes sold in pharmacies [171].

Two studies reported different results regarding the use of NSPs by IDUs. In the state of New York in the United States, NSP participation increased after the programme was legalized [182], but in the state of Connecticut NSP participation decreased after the law was changed to allow the sale, purchase and possession of needles and syringes without a medical prescription and to enable the implementation of NSPs . However, the observed drop in the number of visits to and the number of clients using the New Haven NSP from the month the new decriminalization measure came into effect was probably due to an increase in the use of pharmacies as a

source of sterile syringes, and possible referral to treatment [183].

There is insufficient evidence to consider that the criterion 'temporal sequence' has been fulfilled.

3.5.5 Biological plausibility

As discussed elsewhere, biological plausibility for sterile needle and syringe programmes is high (Sections 3.1.5 and 3.2.5). There is compelling evidence that the re-use and sharing of injection equipment increases the likelihood of HIV infection. It has also been demonstrated that providing sterile needles and syringes with considerable encouragement to only inject with such equipment reduces both risk behaviour and HIV infection. Therefore, there is an inherent biological implausibility that measures that reduce the availability of sterile injecting equipment could be expected to reduce HIV infection. This conclusion is supported by two HIV outcome studies, [61, 180] which have demonstrated reduced availability of sterile needles and syringes in restrictive legal environments.

There is insufficient evidence to consider that the criterion 'biological plausibility' has been fulfilled.

3.5.6 Biological gradient

No relevant literature was identified.

There is insufficient evidence to consider that the criterion 'biological gradient' has been fulfilled.

3.5.7 Coherence

In United States, states where legal restrictions on syringe access were repealed such as Connecticut, Maine and New York pharmacy sales increased, self-reported needle-sharing declined and over time HIV incidence and prevalence also declined [61, 180]. There is no evidence to support the hypothesis that restrictive injecting paraphernalia legislation reduces HIV infection.

There is sufficient evidence to consider that the criterion 'coherence' has not been fulfilled .

3.5.8 Experimental evidence

No relevant literature was identified.

There is insufficient evidence to consider that the criterion 'experimental evidence' has been fulfilled.

3.5.9 Reasoning by analogy

In many respects the legislative environment for the commercial sex industry is analogous to injection paraphernalia legislation. In restrictive legislative environments, public health authorities have limited influence over the nature and extent of safer sex behaviour. In more pragmatic legislative environments where HIV control is a higher priority, public health authorities are able to encourage brothel operators and commercial sex workers to virtually eliminate higher-risk sexual behaviour. Similarly, public health authorities in less restrictive legislative environments are able to rapidly establish an effective network of NSPs, pharmacies, vending machines and other outlets for the exchange, sale and distribution of sterile injection equipment. According to this reasoning, injecting paraphernalia legislation could be expected to increase rather than reduce HIV infection.

Legislative environments that restrict the implementation of a public health intervention are unlikely to ever result in the protection of public health.

There is insufficient evidence to consider that the criterion 'reasoning by analogy' has been fulfilled.

3.5.10 Cost effectiveness

Lurie and Drucker [102] have demonstrated that the repeal of injection paraphernalia legislation in the United States would reduce substantially the cost of health care for HIV/AIDS. As discussed above (Sections 3.2.10 and 3.3.10), providing sterile needles and syringes and encouraging their utilization by IDUs has been shown to be cost-effective. Injecting paraphernalia legislation has been demonstrated to restrict the adoption and implementation of a cost-effective intervention. To that extent, injecting paraphernalia legislation may be considered to impede a cost-effective programme.

There is sufficient evidence to consider that the criterion 'cost effectiveness' has not been fulfilled.

3.5.11 Absence of negative consequences

Heimer and colleagues found that following the repeal of legislation that had restricted the sale and possession of needles and syringes in Connecticut, participation by IDUs in the pre-existing New Haven exchange declined [183]. However, as described above,

this could be attributed to a number of other factors, especially increased use of pharmacies.

There is insufficient evidence to consider that the criterion 'absence of negative consequences' has been fulfilled.

3.5.12 Feasibility of implementation, expansion and coverage

More than two decades experience of restrictive injecting paraphernalia legislation in the United States demonstrates that laws of this kind can be implemented and extended to cover most if not all of a large country. Of the 50 states and territories in the United States, 51 jurisdictions recently had paraphernalia laws, 14 had syringe prescription laws or regulations and only 13 had legislation authorizing NSPs [184].

There is sufficient evidence to consider that the criterion 'feasibility of implementation, expansion, and coverage' has been fulfilled.

3.5.13 Unanticipated benefits

No literature was identified showing unanticipated benefits of restrictive injecting paraphernalia legislation.

There is insufficient evidence to consider that the criterion 'unanticipated benefits' has been fulfilled.

3.5.14 Special populations

In Manipur, India a study of current and former IDUs found that fear of arrest and harassment were the main reasons IDUs did not carry their own syringes or bleach [185]. Similarly, IDUs in Malaysia also reported fear of arrest for possessing drug injection paraphernalia as the main reason for sharing syringes [186]. These studies from a developing and a middle-income country are very important, although they do not specifically refer to sub-populations of IDUs.

There is insufficient evidence to consider that the criterion 'special populations' has been fulfilled.

4. DISCUSSION

The AIDS pandemic was first recognized more than two decades ago. Within a few years the causative organism was identified and the enormity of the health, social and economic costs of uncontrolled HIV infections was recognized. In many countries HIV epidemics started among IDUs, spreading rapidly to general populations, and evidence for the effectiveness and safety of some HIV prevention strategies in this population began to accumulate.

Beginning in some developed countries, NSPs were rapidly identified as a valuable strategy for keeping HIV under control among IDUs. Although a wide variety of different activities and operational methods are now subsumed by the term 'needle syringe programme', there is sufficient commonality to allow evaluation of this large and growing literature. Large numbers of research studies with widely differing designs in diverse countries have been reported. An increasing number of countries commenced NSPs and then began to expand them to scale. Although evidence supporting the effectiveness and safety of NSPs grew, HIV has continued to spread even more rapidly among and from IDUs than the adoption and later expansion of NSPs.

Some excellent and comprehensive reviews of the evidence for NSPs have appeared [6, 187-193]. All have confirmed the effectiveness of NSPs in reducing HIV spread. This conclusion was drawn with increasing confidence in more recent reviews as more and better quality data have become available. This study represents the first international review of NSPs. It is also the first systematic review to consider the extent to which evidence for NSPs fulfils the Bradford Hill criteria. These criteria, originally devised to assess inferences of causality drawn from observational studies, have been used increasingly in recent years to assess intervention studies. This review has attempted to apply the Bradford Hill criteria rigorously and conservatively but in so doing has often encountered the problem of 'double negatives' in drawing conclusions. Accordingly, readers are encouraged to review the wording of all conclusions relating to Bradford Hill criteria carefully. Each of these refers specifically to a null hypothesis.

The bleach literature falls into two clear parts: some of the laboratory data are impressive, but there is a depressing consistency about the field study findings, which raise serious concerns about the effectiveness of this approach.

The overwhelming majority of studies evaluating the effectiveness and safety of NSPs are highly supportive. But in spite of the impressive volume and quality of this supporting evidence, some still question the efficacy and safety of NSPs. A somewhat tendentious interpretation of a handful of negative studies from Montreal [65] and Vancouver [66] is relied upon by critics of the proposition that NSPs are effective and safe, despite subsequent papers providing plausible alternative explanations for these negative findings [67, 102-105]. The benefits of NSPs are much easier to demonstrate when these are the only outlets for sterile injecting equipment. Another methodological issue is the tendency for studies to measure baseline and outcome variables dichotomously, substantially reducing the power of these studies.

The quantity and quality of the literature on pharmacy availability of sterile injecting equipment is not as impressive as the literature on NSPs. It is also more difficult to interpret because of the often confounding effect of NSPs and thus not easy to estimate the specific contribution of pharmacy availability. However, studies evaluating pharmacy availability in the absence of NSPs make it abundantly clear that pharmacies are also effective. The paucity of data for vending machines is even more marked than for pharmacies. However, there is a common finding that pharmacy and vending machine outlets often attract a somewhat different population from those attending NSPs. The attitude of pharmacists to IDUs is critical to the success or failure of pharmacy availability of sterile injecting equipment. There is a need to consider outlet density and type more as a system rather than in terms of its component parts.

The literature on the disposal of used injecting equipment is also somewhat disappointing. Although there is no convincing evidence that NSPs have exacerbated the disposal of used injecting equipment in public places, there is little doubt that discarded used injecting equipment seriously undermines the sustainability of this vulnerable intervention that is so critical to public health.

Although the phenomenon of injecting paraphernalia legislation is not unique to the United States, virtually the entire literature on this subject has been generated in that country. It is also hard to interpret this literature because to some extent, the existence and number of NSPs is independent of injecting paraphernalia legislation. Many NSPs have been started without official sanction and sometimes legislative constraints have not existed or have been repealed, and yet few NSPs have been established.

Nonetheless, it is clear that injecting paraphernalia legislation has been a critical obstacle in many states of the United States and this is probably also true, but to a lesser extent, in a number of other countries. Several states in the United States have repealed restrictive laws demonstrating that it is quite feasible to do so. However, several layers of obstacles to the establishment of an effective national NSP system have then often become evident, including an unsupportive federal political environment, compounded by state, city and neighbourhood opposition and additional funding inadequacy. Although these legislative and political problems have been more carefully studied in the United States than in any other country, there are many other countries with similar deep-rooted opposition or ambivalence to effective deployment of NSPs. Legalization of NSPs has improved programme operation, including increasing supplies, staffing, hours of operation, and availability of additional services such as counselling or referral to drug treatment programmes [182, 194, 195].

This review should be considered in the light of several limitations. The only literature reviewed was in the English language. Most of this literature originated from developed countries, which although peer reviewed, may still be subject to one or more forms of publication bias. The overwhelming majority of studies were quantitative and there were very limited qualitative data to illuminate the findings of the quantitative studies. The literature regarding the second term of reference (needle syringe programme effectiveness) is so vast that there is little need to also review the relevant grey literature. Any subsequent reviews of bleach and decontamination, pharmacy and vending machines, disposal and injecting paraphernalia legislation, should make greater use of grey literature. The white literature on these areas is small and often less than impressive in quality.

This review was also inevitably limited by inherent deficiencies in the quality of the existing literature. For example, much of the literature classifies injecting drug users as persons who either attend or do not attend NSPs, whereas in reality this phenomenon is dimensional rather than categorical. In addition, outcome measures are usually categorical, although again the phenomenon is usually dimensional. For example, sharing is usually measured as either present or absent during a particular period, rather than estimated on a continuum [103].

5. CONCLUSIONS

5.1 There is compelling evidence that increasing the availability and utilization of sterile injecting equipment by IDUs reduces HIV infection substantially.

Overall, there is convincing evidence that NSPs, assessed conservatively, fulfil six of the nine Bradford Hill criteria (strength of association, replication of findings, temporal sequence, biological plausibility, coherence of the evidence and argument by analogy) and all of the five additional criteria (cost effectiveness, absence of negative consequences, feasibility of implementation, expansion and coverage, unanticipated benefits and special populations). Measured against any objective standards, the evidence to support the effectiveness of NSPs in substantially reducing HIV must be regarded as overwhelming.

5.2 There is no convincing evidence of any major, unintended negative consequences.

Specifically and after almost two decades of extensive research, there is still no persuasive evidence that needle syringe programmes increase the initiation, duration or frequency of illicit drug use or drug injecting.

5.3 Needle syringe programmes are cost-effective.

It is more difficult to generalize from studies of cost effectiveness of needle syringe programmes in one country to other similar countries, let alone from developed countries to resource-poor settings. However a number of careful studies in several developed countries and some transitional countries have demonstrated convincingly that needle syringe programmes are cost-effective.

5.4 Needle syringe programmes have additional and worthwhile benefits apart from reducing HIV infection among IDUs.

There is reasonable evidence that needle syringe programmes can increase recruitment into drug treatment and possibly also into primary health care.

5.5 Bleach and other forms of disinfection are not supported by good evidence of effectiveness for reducing HIV infection.

The evidence supporting the effectiveness of bleach in decontamination of injecting equipment and other forms of disinfection is weak. Field studies cast considerable doubt on the likelihood that these measures could ever be effective in operational conditions, notwithstanding the strength of the laboratory data. At best, these strategies can only be regarded as acceptable in community or correctional settings where the introduction of NSPs is considered impossible because of fear or hostility on the part of community members or authorities. Public health practitioners in these settings should continue to advocate for the introduction of NSPs as the most reliable and evidence-based way of maintaining control of HIV among IDUs. Bleach and disinfection fulfilled only two of the nine Bradford Hill criteria (biological plausibility and analogy) and three of the five additional criteria (absence of negative consequences, feasibility of implementation, expansion and coverage, and special populations).

5.6 Pharmacies and vending machines increase the availability and probably of the utilization of sterile injecting equipment by IDUs.

There is reasonable evidence that pharmacy availability of sterile injecting equipment does provide specific benefits in addition to those derived from NSPs. The population attending pharmacies tends to be less disadvantaged than those attending community- based NSPs, although there is often some considerable degree of overlap. Pharmacy schemes complement the benefits of NSPs although some jurisdictions have relied entirely on pharmacy-based outlets. Vending machines increase access in some geographical locations, to some special populations and at times of the day that are otherwise difficult to provide for. Pharmacy and vending machines fulfilled six of the nine Bradford Hill criteria (strength of association, replication, temporality, biological plausibility, coherence and analogy) and four of the five additional criteria (cost-effectiveness, absence of negative consequences, feasibility of implementation, expansion and coverage and special populations).

5.7 Injecting paraphernalia legislation is a barrier to effective HIV control among IDUs.

Injecting paraphernalia legislation has been a major obstacle to HIV control among IDUs in many states of the United States (and a less well-documented but probable obstacle in some other countries). This legislation has impeded the establishment of a timely and appropriate public health response to the HIV epidemic. In terms of the available evidence that restrictive injecting paraphernalia legislation helps to control HIV infection among IDUs, only two of the nine Bradford Hill criteria (specificity and analogy), and one of the five additional criteria (feasibility of implementation, expansion and coverage) were fulfilled. There is evidence that repeal of this legislation results in worthwhile public health benefits.

5.8 Needle syringe programmes on their own are not enough to control HIV infection among IDUs.

There is no evidence of a protective effect for single interventions strong enough to guarantee HIV control but the aggregate effect of several harm-reduction interventions appears to be generally successful in maintaining HIV control. Sterile needle and syringe availability needs to be considered as a system and has to be supported by a range of complementary measures if communities wish to control HIV infection among and from IDUs.

6. RECOMMENDATIONS

6.1 The studies reviewed in this report present a compelling case that NSPs substantially and cost effectively reduce the spread of HIV among IDUs and do so without evidence of exacerbating injecting drug use at either the individual or societal level. This suggests that authorities responsible for areas threatened by or experiencing an epidemic of HIV infection among IDUs should adopt measures urgently to increase the availability and utilization of sterile injecting equipment and expand implementation to scale as soon as possible. As an approximation it is reasonable to assume that providing 200 sterile needles and syringes per drug injector per year is a figure that is achievable and likely to control HIV infection in this population. It may take several years, starting from scratch, to reach this figure. Higher targets may be needed where seroprevalence has already reached unacceptable levels. The precise quantity of injecting equipment required is not known. Cocaine injectors require more needles and syringes than heroin injectors.

6.2 The higher the seroprevalence of HIV among IDUs, the more HIV sexual transmission becomes an important factor. HIV sexual transmission is more difficult to control than HIV spread through sharing of injection equipment.

6.3 Carefully evaluated pilot programmes of NSPs have their place in allowing the introduction of this invaluable protection of public health but they also possess certain risks. Firstly, the case for NSPs is already so compelling and the international experience so impressive, that there is no longer any real justification for pilot programmes. Pilot programmes may further delay the much-needed expansion phase. If the programme remains frozen at the pilot phase level of implementation, then there is a risk that the programme will remain chronically underfunded, with attendant inadequate coverage.

6.4 NSPs are only one way of increasing the availability of sterile injection equipment and these exist in many forms around the world. Some cities require 'one-for-one' exchange, others attempt to achieve high levels of exchange but accept less than 100%, while authorities in other jurisdictions provide sale or free distribution without attempting to remove used injection equipment from circulation. There is no evidence that any one method is notably more efficacious or cost effective. Many jurisdictions have found that a diversity of approaches is optimal, with some methods working best in certain locations and conditions and other approaches better suited in other places and conditions. The important point is to aim to reduce the circulation time of needles and syringes.

6.5 Attempts to increase the availability of sterile injecting equipment should be accompanied by endeavours to increase the utilization of sterile injection equipment, reduce the utilization and availability of un-sterile injection equipment and improve the appropriateness of discarding used injecting equipment. These objectives are best met through education of IDUs where peer based, explicit campaigns have generally been found to be highly effective.

6.6 However worthwhile it may be to increase the availability and utilization of sterile injecting equipment with the aim of controlling HIV infection among IDUs, this appears to be a necessary rather than a sufficient intervention. Other activities that complement the benefits of sterile injecting equipment programmes include education of IDUs, increasing the capacity, range and quality of drug treatment (especially substitution treatment) and community development of drug users.

6.8 Pharmacy-based NSPs appear to complement community-based schemes and may provide access to a somewhat different population of IDUs. Vending machines increase coverage geographically and across time zones but have the disadvantage of not providing information, counselling or referral.

6.9 Special populations of IDUs are of great public health significance in HIV control especially "bridge" populations (such as IDUs who are also men who have sex with men or male or female commercial sex workers). In most countries, a large proportion of IDUs spend a considerable proportion of their drug-injecting careers behind bars while a large proportion of prison inmates have a history of drug injecting. Many inmates of correctional facilities continue to inject while they are incarcerated. The limited evidence available from evaluation of the few existing prison NSPs suggests that their benefits are similar to community programmes, while there is no evidence to date that these programmes are inherently unsafe or counter-productive. On the available evidence, there is a strong case for establishing and expanding NSPs in correctional facilities in many countries.

6.10 Disinfection and decontamination schemes are not supported by evidence of effectiveness and should only be advocated as a temporary measure where there is implacable opposition to NSPs in certain communities or situations (e.g. correctional facilities).

6.11 This review has demonstrated significant gaps in research. The quantity and quality of research needs to be improved in bleach and disinfection field studies, pharmacy and vending machine evaluation, measures to reduce inappropriate disposal and injecting paraphernalia legislation in countries other than the United States. More and better qualitative research would illuminate the findings of the numerous quantitative studies. Research should make more use of continuous measures of baseline characteristics, interventions and outcome variables. However, it is important to recognize that the limited implementation of NSPs is not fundamentally due to a lack of adequate research data. Therefore, it is unlikely that increasing the quantity of the same kind of research that already exists is unlikely to increase the implementation of NSPs.

Table 1. Summary of field studies of bleach and HIV

Study	Setting / Intervention:	Outcome: use of bleach	Outcome: HIV risk/prevalence	Comment
Chaisson, et al. 1987 [14]. San Francisco	Distribution of bleach (5.25% concentration) with instructions, to IDUs. Also used posters and billboards to promote use of bleach to prevent HIV infection.	Comparing 1987 (after intervention) with 1985 (pre-intervention): ◗ Use of bleach increased (47% vs 6%). ◗ Proportion never using bleach decreased (76% vs 36%). ◗ % sharing needles remained the same	Prevalence of HIV infection increased from 10% (1985 pre-intervention) to 15% (1987 post-intervention).	Modification of sterilization practice occurred in IDUs in treatment (who were not primary target of programme). Conclusion: bleach should only be promoted in conjunction with other risk-modification measures, such as widespread availability of sterile needles and syringes.
Vlahov, Astemborski, et al. 1994 [17]. Baltimore, Maryland.	Follow-up of seronegative IDUs (1988- 1992) in setting of bleach/alcohol promotion.	46% of IDUs used disinfection all the time	Disinfection had no protective effect for IDUs who used all the time vs IDU who used less than all the time or never. **Disinfection use** / **HIV seroconversion OR (95%CI)** None: 1 Less than all the time: 1 (0.36 - 2.82) All the time: 0.87 (0.32 – 2.37)	Conclusion: Over-reliance upon bleach or alcohol disinfection in prevention of new HIV infection among IDUs is unsafe.
Titus, Marmor, et al. 1994 [16]. New York City.	Follow-up of seronegative IDUs in setting of bleach/alcohol promotion (reinforced after each research interview). Multi-ethnic	Behaviour change may be enabled by counselling sessions (conducted at the end of interview session) – repeated counselling increased recall.	Use of bleach had no significant effect on risk of HIV seroconversion. **Disinfection use** / **HIV seroconversion OR (95%CI)s** Never: 1 Sometimes: 6.55 (0.8 – 55.8)* Always: 1.05 (0.1 –15.9) * The (non-significant) increased risk for IDUs who sometimes used bleach, was not significant after injection frequency was adjusted for.	Efforts to slow transmission of HIV among IDUs should not emphasize bleach.

Table 2. Laboratory evidence of effect of bleach (hypochlorite) on HIV

Study	Year	Virus(cell assoc/free)	Medium	Dilution	Contact Time	Inactivated Y/N	Comment
Abdala, et al. 2001 [34]	2001	Cell-assoc and cell free together 2-20 μL of blood		undiluted	5 sec	yes[1]	Recovery of HIV dependant on blood vol. in syringe, number of rinses, and titre of HIV in blood.
Aranda-Anzaldo, et al. 1992 [46]	1992	Cell-free		1% 20% undiluted?	30 sec 60 sec 30 sec	Yes No Yes	HIV inactivation depends on concentration and incubation time.
Contoreggi et al. 2000 [51]	2000	Cell assoc(?) Cell assoc(?)	Cult medium Cult medium	High Low		Yes No[2]	Suggests that sharing of a bleach-cleaned syringe may increase likelihood of transmitting HIV-1.
Druce et al., 1995 [40]	1995	Cell free Cell assoc Cell assoc	Cell cult medium Suspended in blood Suspended in blood	2500 ppm 25 000 ppm 2500 ppm 25 000 ppm 25 000 ppm	60 sec 60 sec 5 sec	Yes No Yes	Effectiveness compromised by presence of blood
Druce et al. 1995 [39]	1995	Cell assoc			10 sec[3]	Yes	30 sec required if syringe left for 3 hours at room temp. Increase thought to be due to presence of dried and clotted blood.
Flynn et al. 1994 [42]	1994	Cell-assoc Cell-assoc	Cult medium Suspended in blood	Neat, 1:10; 1:100	60 sec 60 sec	Yes No	
Gordon et al. 1993 [45]	1993			undiluted?	30 sec	Yes	
Martin et al. 1985 [49]	1985	Cell-free		0.1%	2 min	Yes	

[1] Not to zero; (HIV still able to be recovered from 1/153 syringes)
[2] Facilitated growth
[3] Needle/syringe surface

Study	Year	Virus(cell assoc/free)	Medium	Dilution	Contact Time	Inactivated Y/N	Comment
Newmeyer et al. 1990 [47]	1990	Cell-free		Full strength	60 sec	Yes	
Resnick et al. 1986 [48]	1986			10% dilution	60 sec	Yes	
Shapshak et al. 1993 [44]	1993			Undiluted?	30 sec	Yes	
Shapshak et al. 1994 [41]	1994	Pelleted cell assoc 50μL of blood Pelleted cell assoc 50μL of blood Pelleted cell assoc 50μL of blood Pelleted cell assoc 50μL of blood	Undiluted Diluted Undiluted 10%	30 sec 30 sec 15 sec 2 min	Yes No No Yes		
Spire et al. 1984 (50)	1984		8% serum	Undiluted? 100 ppm	30 sec 30 sec	Yes Yes [4] (3.75log $TCID_{50}$ HIV/ml)	
Van Bueren et al. 1995 [36]	1985		80% serum 80% blood	500 ppm 1000 ppm 2500 ppm	1-2 min	Yes [5] (>4log$TCID_{50}$ HIV/ml) No [6] (3.75log$TCID_{50}$ HIV/ml) Yes [7] (1.5log$TCID_{50}$ HIV/ml)	Results stress importance of cleaning prior to infection. Bleach maybe ineffective in the presence of organic matter. If prior cleaning not possible, use high concentration of chlorine (min. 10000 ppm available chlorine)
Weber et al. 1999 [35]	1999		No blood No blood 80% blood	5000 ppm (1:10 bleach dilution) 500 ppm (1:100 bleach dilution) 5000 ppm	30 sec [8] 30 sec 10 min	Yes Yes No	HSV (not HIV) used, but has similar susceptibilities.

[4] 3.75 log TCID HIV/ml
[5] > 4 log TCID HIV/ml
[6] 3.75 log TCID HIV/ml
[7] 1.5 log TCID HIV/ml
[8] Environmental spills – cleaning of blood spills

Table 3a. Efficacy of needle syringe programming. NSP use and HIV seroprevalence or seroconversion as outcomes: studies with positive findings

Study	Respondents	Outcome variables	Results
Ljungberg et al., 1991 [59]. Skane province, Sweden; observational study.	182 "active participants" of NSP	Seroprevalence in south Sweden compared with Scandinavian sub-populations with comparable drug problems.	HIV seroprevalence among IDU in south Sweden maintained at ~1% contrasted with up to 60% in other Scandinavian sub-populations.
Heimer et al., 1993 [60]. New Haven, USA.	Random sample of returned syringes at the New Haven NSP.	Percentage of syringes containing HIV.	Within three months of initiating syringe exchange, percentage of syringes containing serum with HIV declined by one third.
Des Jarlais et al., 1996 [61]. New York City, USA; prospective cohort study using pooled data from three studies in a high prevalence area.	601 IDUs at several exchange sites.	HIV incidence among continuing NSP users compared with non-users.	Multivariate proportional-hazards analysis, not using an NSP was associated with a Hazard Ratio of 3.35 (95% CI 1.29, 8.65) for incident HIV compared with using an NSP.
Hurley et al., 1997 [62]. ecological study of 81 cities between 1988 and 1993.	Data from reports on HIV seroprevalence linked with details of NSP implementation in 81 cities world-wide.	HIV seroprevalence among IDU in 52 cities with NSP compared with that in 29 cities without NSPs.	On average HIV seroprevalence increased by 5.9% per year in cities without NSPs and declined by 5.8% per year in cities with NSPs. Average annual change in seroprevalence was 11% lower in cities with NSPs (95% CI –17.6 to –3.9, p=0.004).
Monteroso et al., 2000 [63]. Five United States cities; observational study.	Some 2306 street IDUs recruited from 5 United States cities and a state women's prison and followed up eight months later.	HIV incidence among NSP participants compared with non-participants.	Participation in NSPs associated with substantially reduced risk of HIV acquisition, but not statistically so.
Health Outcomes International (HOI), 2002 [64]. Ecological study of 778 calendar years of data from 103 cities worldwide.	Details of NSP implementation and HIV seroprevalence measurements for 67 cities without NSP, 36 cities with NSP.	HIV seroprevalence compared in cities with and without NSPs.	HIV seroprevalence in cities with NSPs declined by a mean annual 18.6% compared to an 8.1% increase in cities without NSPs.

Table 3b. Efficacy of needle syringe programming. NSP use and HIV seroprevalence or seroconversion as outcomes: studies with negative findings

Study	Respondents	Outcome variables	Results
Bruneau et al., 1997 [65]. Montreal, Canada; nested case-control study.	408 treated and untreated IDU; any versus no NSP use, last 6 months.	HIV seroconversion	Exclusive NSP users four times more likely to seroconvert than never-users. OR=4.2 (95% CI, 1.5-11.5). Non-exclusive NSP users three times more likely to seroconvert than never-users. OR=3.3 (95% CI, 1.6-6.7). Consistent NSP use strongly associated with seroconversion. OR=10.5 (95% CI, 2.7-41.0).
Bruneau et al., 1997 [65]. Montreal, Canada; prospective cohort study.	1599 treated, untreated IDU. NSP users compared with non-users. Mean follow-up period 21.7 months.	HIV seroconversion	Substantially increased risk of HIV seroconversion associated with NSP use. AOR=2.2 (95% CI, 1.5-3.2).
Strathdee et al., 1997 [66]. Vancouver, Canada; observational study.	1006 untreated IDU. Frequent NSP attenders compared to non-attenders.	HIV seroprevalence.	Frequent NSP attenders more likely to be HIV positive than non-attenders.

Table 3c. Efficacy of needle syringe programming. NSP use and HIV seroprevalence or seroconversion as outcomes: studies with indeterminate findings

Study	Respondents	Outcome variables	Results
Patrick et al., 1997 [68]. Vancouver, Canada; case-control study.	281 untreated IDU. Ever-users of NSP compared with never-users.	HIV seropositivity	No association between ever using a NSP and HIV seropositivity.
Schechter et al., 1999 [67]. Vancouver, Canada. prospective cohort study.	694 treated and untreated IDU followed for 15 months. Frequent attenders vs infrequent NSP attenders.	HIV incidence	No differences in HIV incidence between frequent attenders and infrequent attenders.

Table 4a Efficacy of needle syringe programming. NSP use and HIV risk behaviour outcomes: studies with positive findings.

Study	Respondents	Outcome variables	Results
Hartgers et al., 1989 [69] Amsterdam, the Netherlands; observational study.	145 untreated IDUs in community sample. NSP users vs non-users.	Syringe borrowing	NSP users less likely to borrow than non-users in previous month (10% compared with 23%) and also in previous 2 years (33% compared with 57%).
Donoghoe et al., 1989 [70]. Scotland and England; prospective cohort study, pre-post (2 months) comparison.	282 NSP users and non-NSP control group.	Syringe-sharing	Significant decline in syringe-sharing among NSP users in previous month compared with no change in control group.
Kaplan et al., 1991; Kaplan et al., 1994; Kaplan et al., 1995 [98-100]. New Haven, USA; syringe tracking and modelling studies.		Syringe exchange rate, syringe return rate, syringe circulation time	The syringe exchange rate per IDU and the return rate of programme syringes both increased, implying a decreased mean circulation time for each syringe.
Frisher & Elliott, 1993 [71]. Glasgow, Scotland; observational study	503 IDU community sample. NSP users in last 6 months vs non-users.	Syringe borrowing or lending	NSP attenders less likely (mean 4.5 times/mo) than non-attenders (mean 9.2 times/mo) to borrow used syringes, despite legal pharmacy sale of syringes.
Keene et al., 1993 [72]. Wales, UK; observational study	328 mostly untreated IDU. NSP attenders vs non-attenders.	Syringe-sharing in last year and last 4 months	NSP attenders less likely to share syringes in last year and last 4 months.
Watters et al., 1994 [73]. San Francisco, USA; observational study	752 treated, untreated IDU. NSP users vs non-users.	Syringe-sharing Injection frequency	NSP use was strong independent predictor of not sharing syringes. OR=0.71 (95% CI, 0.59-0.87). Median number of injections declined following NSP attendance, from 1.9 injections/day to 0.7 injections/day
Des Jarlais et al., 1994 [74]. New York City; multiple cross-sectional study.	1115 IDU entering methadone treatment.	Syringe borrowing, lending	Quarterly level of NSP use correlated negatively with proportion of IDU reporting borrowing and lending of syringes ($X_=-0.67$, $p<0.02$ and $X_=-0.44$, $p<0.13$ respectively).
Oliver et al., 1994 [75]. Portland, USA; prospective pre-post NSP evaluation study.	115 NSP clients, pre-and post-NSP attendance. No comparison group.	Syringe sharing, renting and borrowing	Substantial decline in sharing (20% to 7%), renting (9% to 3%) and also borrowing of syringes.

Study	Respondents	Outcome variables	Results
Oliver et al., 1994 [75]. Portland, USA; prospective cohort study.	412 untreated IDU followed for 6 months. NSP users compared to outreach IDU.	Syringe borrowing	NSP users borrowed less and outreach clients (who bleached more).
Paone et al., 1994 [76]. New York City; retrospective pre-post comparison study.	1269 NSP clients	Syringe borrowing	Substantial decline in borrowing used syringes (from 29% to 12%) and in renting or buying a used syringe (from 22% to 6%).
Peak et al., 1995 [77]. Kathmandu, Nepal; multiple cross-sectional study.	586 NSP clients	Number of sharing partners and sharing occasions.	Median number of sharing partners declined from 2 to 1 and median number of sharing occasions declined from 14 to 2 following NSP attendance.
Guydish et al., 1995 [78]. San Francisco, USA; observational study	50 NSP clients; compared number of months since first used NSP.	Number of sharing partners	Recent NSP users had fewer sharing partners and number of sharing partners was negatively correlated with number of NSP visits in past 30 days.
Schoenbaum et al., 1996 [79]. New York City; prospective cohort study.	329 treated IDU, NSP users compared with non-users.	Syringe-sharing	NSP users significantly less likely than non-users to report syringe sharing 4 years after the NSP was introduced.
Vlahov et al., 1997 [80]. Baltimore, USA; prospective cohort study.	221 NSP clients pre-NSP, 2 week, 6 month, follow-ups. No comparison group.	Syringe-borrowing, -lending and indirect sharing	Substantial declines in syringe borrowing (22% to 8%) and syringe lending (27% to 12%).
Singer et al., 1997 [81]. Hartford, USA; multiple cross-sectional study.	710 untreated IDU; Pre-post comparison.	Syringe reuse (a proxy for syringe sharing)	Respondents significantly reduced their 'reuse' of syringes following introduction of NSP and legalization of pharmacy sale of syringes.
Guydish et al., 1998 [82]. San Francisco, USA; observational study	114 NSP clients; Compared on basis of proportion of syringes	Syringe-sharing	Those who obtained a higher proportion of syringes from the NSP 92% vs 81% were less likely to report the sharing of syringes.
Heimer et al., 1998 [83]. New Haven, San Francisco, Baltimore and Chicago; retrospective analysis of data.	Large sample of NSP attenders; first visit data compared with later visits.	Syringe reuse	Self reported reuse of injection equipment declined by at least half in three of the four cities. In the fourth city different methods of data collection (including syringe tracking) corroborated these findings.

Study	Respondents	Outcome variables	Results
Gleghorn et al., 1998[84]. Seven metropolitan centres, USA; observational study.	Broad sample of IDUs.	Source of most recent syringe (reliable/unreliable)	IDUs were most likely to have used a reliable source to obtain their most recent syringe in cities with a NSP. OR=5.3 (95% CI 3.3-8.5).
Bluthenthal et al., 1998 (85). Oakland, USA; observational study.	1304 untreated IDU in community sample. Compared NSP users with non-users.	Syringe-sharing	NSP use conferred a greater than 40% protective effect on syringe sharing. AOR=0.57 (95% CI 0.46-0.72).
Bluthenthal et al., 2000[86]. Oakland, USA; controlled cohort study.	340 high-risk IDU. NSP users compared with non-users.	Syringe-sharing cessation	IDU who began using the NSP were more likely to stop sharing than non-users (AOR=2.68; 95% CI, 1.35-5.33), as were IDU who continued using the NSP (AOR=1.98; 95% CI, 1.05-3.75).
Cox et al., 2000[87]. Dublin, Ireland; evaluation study of NSP.	IDU who attended the NSP; compared data at first visit and 3 months later.	Sharing of injection paraphernalia.	Significant reductions in borrowing and lending of syringes.
Monterroso et al., 2000[63]. Five United States cities and a State Women's prison; prospective study.	2306 street IDUs; NSP participants compared with non-participants. 8 months follow-up.	Syringe reuse	Reported use of NSP was significantly associated with not using previously used needles. (ORadj=2.08; 95% CI, 1.15-3.85, p=0.015).
Power et al., 2002[88]. Sverdlovsk Oblast, Russia; short-term process evaluation of three NSPs.	IDU attenders compared with non-attenders 6 months after NSP opened.	HIV risk behaviours	NSP attenders reported less HIV risk behaviour than non-attenders. The following risk behaviours were statistically significant at P<-.0005: only use own syringe; only use own needle; only use own filter; only use own drug solution; use another's syringe for measuring drug dose.
Gibson et al., in press[90]. San Francisco; prospective cohort study.	259 IDU followed for mean period of 10.7 months. NSP users compared with non-users.	HIV risk behaviour	NSP use had a substantial protective effect against HIV risk behaviour (a two-fold decreased odds of HIV risk behaviour), compared with non-use. Controlled for baseline risk behaviour and exchange use as markers of risk-taking tendency, and other potential confounders.

Table 4b. Efficacy of needle syringe programming. NSP use and HIV risk behaviour outcomes: studies with negative findings.

Study	Respondents	Outcome variables	Results
Klee et al., 1991 [91]. Northwest England, UK; observational study.	217 treated, untreated IDU; Regular NSP users compared with rare or never users.	Syringe lending	Regular use of NSP associated with passing of syringes.

Table 4c. Efficacy of needle syringe programming. NSP use and HIV risk behaviour outcomes: studies with indeterminate findings

Study	Respondents	Outcome variables	Results
Donoghoe et al., 1992 [92]. London, UK; observational study.	207 untreated IDU; NSP users compared with non-users.	Syringe-sharing	NSP users and non-users equally likely to share used injection equipment.
Hartgers et al., 1992 [93]). Amsterdam, the Netherlands; observational study.	131 HIV-seronegative IDU; mostly NSP users	Syringe-borrowing	Regular NSP use not associated with increased or decreased borrowing.
Van Ameijden et al., 1992 [97]. Amsterdam, the Netherlands; case-control study.	232 untreated IDU; NSP users compared with non-users.	Proportion of syringes exchanged	No protective effect associated with proportion of syringes exchanged at the NSP.
Van Ameijden et al., 1994 [94]. Amsterdam, the Netherlands; observational study.	Community sample of 616 treated, untreated IDU. NSP users compared with non-users, previous year.	Syringe borrowing and lending	Bivariate negative association with borrowing and lending of syringes. Later multivariate analysis (1998) adjusted for possible confounders discounted these negative findings.
Klee et al., 1995 [95]. Northwest England, UK; observational study.	Community sample of 663 treated, untreated, opiate, non-opiate IDU in three studies; Regular NSP users compared	HIV risk behaviour	Mixed pattern of NSP use and HIV risk behaviour in three studies.
Van Haastrecht et al., 1996 (101). Amsterdam, the Netherlands; prospective cohort study.	632 treated, untreated IDU followed over 8 years; NSP users compared with non-users.	Predictors of mortality among HIV positive and HIV negative IDU.	Mortality rate of NSP attenders about the same as that for non-attenders.
Van Ameijden et al., 1998 [96]. Amsterdam, the Netherlands; observational study.	Community sample of 879 treated, untreated IDU seen at 6645 visits; NSP users compared with non-users, previous year.	Syringe borrowing and lending	Irregular NSP users at statistically greater risk of borrowing and lending of syringes than regular users or non-users.

Table 4d. Tally of studies finding positive versus negative or null effects of syringe exchange broken down by presence or absence of legal access to pharmacy syringes[1] (89)

		Positive	Negative/null	Total
Legal pharmacy access?	Yes	5	13	18
	No	7	0	7
Total		12	13	25

[1] Relationship between positive versus negative or null findings and legal pharmacy access significant by Fisher's exact test at $p<0.002$.

Table 5. Impact of pharmacy sale of syringes upon HIV prevalence, incidence and risk behaviours

Intervention study	Respondents	Outcomes	Results
Caslyn et al., 1991 (162) Seattle, Washington State	Structured interviews with 313 IDUs receiving treatment.	Sharing equipment Median number of people shared syringes with	Significantly less sharing when main source of syringes is the pharmacy (16.2%) compared with other sources (30.6%) ($p<0.01$) IDUs who obtained needles from pharmacies shared with significantly fewer people (median-2.0) than IDUs who obtained needles from other sources (median-3.0) ($p<0.05$)
Gleghorn et al., 1995 (119). Baltimore, Maryland, USA.	Structured interviews with 466 IDUs	Pharmacy as usual source of needles & syringes	IDUs were less likely to use shooting galleries: (AOR 0.33; 95%CI 0.14, 0.75) and less likely to have been in jail (AOR 0.45; 95%CI 0.23, 0.87) (add comparison group)
Groseclose et al ., 1995 (164). Connecticut, USA.	Structured interview with IDUs before and after legalization of purchase and possession of syringes.	Syringe sharing Ever shared syringes Obtaining syringes from street	A substantial decrease from 52% to 31% A substantial decrease from 68% to 52% A substantial decrease from 88% to 74%
Hunter et al., 1995 (163). London (metropolitan area), UK.	Annual survey of ~515 IDUs over 4 years.	HIV prevalence	A substantial decrease in HIV prevalence among IDUs from 12.8% in 1990 to 6.9% in 1993

Intervention study	Respondents	Outcomes	Results
Ingold & Ingold, 1989[161]. Paris, Bordeaux, Marseille, France.	Structured interview of 280 IDUs from street and in treatment.	No syringe sharing	Liberalization had significant impact on behaviour of IDUs, with 52% street sample, 40% in treatment purchased syringes from pharmacies and never shared with others
Nelson et al., 1991[117]. Baltimore, United States	Structured interview with 2921 IDUs.	HIV seroprevalence Used equipment no one else had used *greater than half the time* Used equipment used by someone else *less than half the time* Shared needles>1 person	A significantly lower proportion of diabetic IDUs (9.8%) had HIV compared with non-diabetic IDUs (24.3%) (p=0.03). Significantly more diabetic IDUs (77%) shared less than non-diabetic IDUs (64%) (p<0.05) Significantly more diabetic IDUs (90%) did not use equipment after someone else compared with non-diabetic IDUs (78%) (p<0.01) A lower proportion of diabetic IDUs (37%) shared needles compared with non-diabetic IDUs(48%) (p<0.14)
Richard et al., 2002[167]. Houston, Texas	Structured interviews with 108 IDUs.	Inject after person that is not sexual partner Has new syringes	Less likely when IDU has a new syringe: AOR 0.236 (95%CI 0.06, 0.89) More likely to be a heroin user (AOR 1.49; 95%CI 1.18, 1.88) and have higher social desirability score (AOR 1.69; 95% CI 1.11, 2.56)
Syringe vending machines			
Heinemann & Gross, 2001[166]. Cross-sectional study of IDUs in prison	Hamburg, Germany	HIV seroprevalence Needle-sharing	No cases identified during program Decreased significantly
Obadia et al.., 1999[165]. Questionnaires applied to 343 IDUs	Marseille, France	HIV seropositivity	IDUs whose primary source of syringes is from SVM are less likely to have positive HIV (OR 0.5; 95%CI 0.2, 0.9) not significant after adjustment

Table 6. Summary of studies on the disposal of needles and syringes

Study	Description	Study objective	Outcomes
Toews et al., 1995 [197]. Florida, USA.	Containers provided by hospital and Public Health Units (PHU). Publicity re project by brochure & local paper advertisements, disseminated by the Chamber of Commerce, Social Services Officer, and PHU.	To provide highly visible and easily accessible disposal containers (in public places and private dwellings)	Annual costs: <US$200 Well accepted by community. Relationship between PHU and community strengthened.
Zamora et al., 1998 [198]. Madrid, Spain.	Presence of HIV-1 assessed in 28 syringes discarded in public places, 10 from NSP, and 10 controls (of which 5 had blood from HIV positive patient, and 5 had blood from HIV negative patient).	To assess the presence of HIV-1 in discarded syringes in public places (and compare to those from NSP)	Little or no risk of HIV-1 infection by casual needle injury from a discarded syringe left by an IDU in a public place.
Springer et al., 1999 [199]. New York City.	Qualitative exploration of syringe disposal interventions for injecting drug users (IDUs) – interviews with injecting and non injecting community members.	To gauge IDUs' and non-IDUs' support for NSPs as syringe disposal interventions.	Non-IDUs favoured a one-way drop box, but IDUs identified fear of arrest for possession of syringes as an important obstacle to use of drop box.
Riley et al., 1998 [200]. Baltimore, USA.	To assess acceptability and use of a community-based needle and syringe disposal intervention.	3 red drop boxes provided for disposal of used needles and syringes in high IDU area. Acceptance of boxes measured by focus groups of residents, IDUs and police - before and after project implementation. Use was measured by weekly counts of needles (in boxes and public places); sample of all deposited needles was randomly chosen for needle washing and subsequent HIV antibody testing.	In the first 10 months, 2971 needles were collected. Of 156 needles tested, 10.9% were positive for HIV antibody. Needle counts on the street did not change in box areas compared with control areas. Red boxes were accepted by the community and drug users. Police officers also used the boxes to dispose of confiscated needles. All focus groups expressed support of project expansion.
Macalino et al., 1998 (201). Baltimore, Maryland, USA	To review issues related to discarded syringes in the community and to describe community-based programmes for the safe disposal of used needles and syringes.	Literature review to identify community-based syringe disposal programmes (other than NSP). Workshop held.	15 programmes for the safe disposal of syringes were identified in Australia, Canada and the United States – only 3 primarily for IDUs. For IDUs, criminal penalties for possession of syringes are a substantial deterrent to participation in community-based efforts to improve safe disposal of used syringes.

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GLOSSARY*

BACKLOADING	Transferring the drug from one syringe to another by removing the plunger from the receiving syringes.
BOOTING	Booting is the practice performed after registering and administering the drug solution. In this process, with the needle still in the vein, the injector draws back on the plunger of the syringe to fill the barrel with blood and then re-injects the blood, sometimes repeating this practice several times. More commonly reported with cocaine than with heroin injection, this practice allegedly enhances the euphoria associated with the drug's effects.
FRONTLOADING	The parcelling out of individual portions from a mixer/ distributor's syringe to the other participants' syringes by removing the needles from the receiving syringes.
RCT	Randomized Controlled Trial
REGISTERING	Registering means that once a needle is inserted, the drug user will draw back the plunger of the syringe to examine for the presence of blood to ensure that theneedle has been properly placed into the vein.
SHOOTING GALLERY	A clandestine location where injecting drug users go to rent needles and syringes. Since used syringes are returned to a common container to be rented again, this process amounts to anonymous sharing of needles and syringes.

** Definitions from Normand et al. (1995)[6]*

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